ARCHIVES OF SURGERY

VOLUME 57 SEPTEMBER 1948 NUMBER 3

COPYRIGHT, 1949, BY THE AMERICAN MEDICAL ASSOCIATION

TREATMENT OF TETANUS

HOMER M. SMATHERS, M.D.

AND

MILTON R. WEED, M.D.

DETROIT

THE CONTROL of tetanic muscle spasms and neutralization of the toxin constitute the aims in treatment of tetanus. Firor and his associates [1] have contributed much to knowledge of the use of antitoxin, but treatment of tetanus is still unsatisfactory and there is a wide disparity in therapeutic regimens employed. It is the purpose of this paper to formulate a plan of treatment based on a review of 82 cases from three Detroit hospitals, including 6 cases in which "intocostrin" (contains raw crude curare), and d-tubocurarine in wax and oil were used in treatment.

Analysis of the entire series is given in table 1. The mortality rate, somewhat higher than reported in other series, is partially explained in table 2, which reveals 36 deaths occurring within forty-eight hours of the time of admission. Nine of the patients died within ten hours, and 1 died in the admitting room.

Table 3 reveals the usual high incidence in the summer months, with fewest cases in the winter.

Analysis of the series with reference to causation, mortality rate and incubation time is given in table 4. The average incubation time was ten days.

The statistics recorded in tables 1, 2 and 3 are similar to those reported by others.[2] Two observations impressed us from the outset: the high rate of mortality and the variety of therapeutic regimens

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

Dr. Smathers is from the Department of Surgery, Wayne University College of Medicine and the Detroit Receiving Hospital, and Dr. Weed is from the Department of Medicine, Wayne University College of Medicine.

1. (*a*) Firor, W. M.; Lamont, A., and Shumacker, H. B., Jr.: Studies in the Cause of Death in Tetanus, Ann. Surg. **111**:246-273 (Feb.) 1940. (*b*) Shumacker, H. B., Jr.; Firor, W. M., and Lamont, A.: Therapeutic Use of Antitoxin in Experimental Tetanus, Surgery **8**:1-18 (July) 1940. (*c*) Firor, W. M.: The Treatment and Prevention of Tetanus, Internat. Abstr. Surg. **75**:185-189 (Aug.) 1942. (*d*) Firor, W. M.: Intrathecal Administration of Tetanus Antitoxin, Arch. Surg. **41**:299-307 (Aug.) 1940.

(Footnote continued on next page)

employed. There were striking differences in the amount and routes of administration of antitoxin, but even greater disparity in the methods employed to control muscle spasms. A review of available knowledge and of the results of treatment employed should enable physicians to standardize treatment and reduce the rate of mortality.

ADMINISTRATION OF ANTITOXIN

That early use of antitoxin is life saving is well established. All but 3 of our patients were given antitoxin in amounts varying from 20,000 to 600,000 units. Two of the 3 died before treatment could be

TABLE 1.—*Analysis of Fifteen Year Period*

No. of Cases	Male		Female		White		Negro		Age		Mortality	
	No.	%	No.	%	No.	%	No.	%	Range	Average	No.	%
82	60	73	22	27	68	83	14	17	13 days to 87 years	22.5 years	49	59.7

TABLE 2.—*Mortality by Twenty-Four Hour Periods*

Hours	24	48	72	96	120	144	144+
Deaths	22	14	4	4	2	2	1
	36						

TABLE 3.—*Seasonal Incidence*

	Winter	Spring	Summer	Fall
Number of cases	6	26	32	18
Number of deaths	4	13	23	9
Percentage of deaths	66	50	72	50

instituted, and for 1 the diagnosis was not made until death. In all but 6, antitoxin was given intravenously. Thirty-seven were given intramuscular injections in addition, and 3 children were treated by the intramuscular route alone. Forty received intrathecal antitoxin in doses of 3,000 to 80,000 units.

Confusion exists as to how much and by what route antitoxin should be administered. All agree that enough antitoxin should be given to neutralize all the unfixed toxin in the body. If, however, one lethal dose has already been fixed, 1,000,000 units will not save an animal. Firor and his co-workers [1a, b] have shown that an initial dose of 50,000 units is more than enough to neutralize several lethal doses of

2. (*a*) Wainwright, J. M.: Tetanus: Its Incidence and Treatment, Arch. Surg. **12**:1062-1079 (May) 1926. (*b*) Deitrich, H. F.: Tetanus in Childhood, with Special Reference to Treatment, Am. J. Dis. Child. **59**:693-710 (April) 1940. (*c*) Vinnard, R. T.: Three Hundred and Fifty-Two Cases of Tetanus, Surgery **18**: 482-492 (Oct.) 1945. (*d*) Pratt, E. L.: Clinical Tetanus, J. A. M. A. **129**:1243-1247 (Dec. 29) 1945.

toxin. After such an initial dose, circulating antitoxin can be demonstrated in the blood for ten to eighteen days.

The most effective route of administration has been contested by clinicians and by laboratory workers. In the uncontrolled series reported by Wainwright [2a] and by Dietrich [2b] the rate of mortality was higher in patients given intrathecal antitoxin. On the other hand, Sherrington,[3] in a series of monkeys given eight lethal doses of toxin, administered antitoxin by different routes with a rate of mortality of 92 per cent after subcutaneous injection, 88 per cent after intramuscular, 72 per cent after intravenous and 44 per cent after lumbar intrathecal administration. Shumacker, Firor and Lamont [1b] also found the intrathecal route more effective than any other in treating animals with early, mild or moderate symptoms. Our results contribute little to the controversy. Of 40 patients given intrathecal antitoxin, 40 per cent survived; in

TABLE 4.—*Causation*

	Number	Percentage	Mortality		Average Incubation Time, Days
			Number	Percentage	
Lacerations	21	25.6	12	57.1	8.8
Puncture wounds	15	18.2	10	66.6	8.1
Unknown	14	17.0	8	57.1	?
Foreign bodies	10	12.2	7	70.0	8.8
Crush or compound fracture	10	12.2	3	30.0	25.0
Leg ulcer	3	3.6	2	66.6	?
Blister	2	2.4	2	100.0	10.0
Gunshot	2	2.4	1	50.0	14.5
Burn	2	2.4	2	100.0	12.5
Self-induced abortion	1	1.2	1	100.0	7.0
Omphalitis	1	1.2	1	100.0	12.0
Vaccination	1	1.2	0	0	7.0

42 patients not given intrathecal antitoxin, 40.5 per cent survived. We believe, however, on the basis of animal experimentation, that 20,000 units should be given intrathecally as soon as the diagnosis is established.

DÉBRIDEMENT

It is obvious that removal of the toxin-producing focus of infection is always indicated if it can be found; yet this procedure is frequently neglected. In this series, débridement was done in 29 cases, with a mortality of 48 per cent; the percentage of deaths in the cases without débridement was 66.

CONTROL OF MUSCLE SPASM

Attempts to control muscle spasm and convulsions have led to employment of a wide variety of drugs. These include muscle paralysants, sedatives and anesthetics.

3. Sherrington, C. S.: Observations with Antitetanus Serum in the Monkey, Lancet **2**:964-966 (Dec. 29) 1917.

Curare.—Shortly after Claude Bernard's studies on crude curare, a few workers [4] attempted to control the convulsions of tetanus with it. These attempts were then abandoned for about fifty years, until revived by Cole,[5] 1934, Mitchell,[6] 1935, and West,[7] in 1936. Cullen and Quinn [8] reported survival of a patient with tetanus treated with curare in 1943 and, in an addendum, 3 similarly treated patients that died. Vinnard [2c] reported the use of curare under the supervision of Adriani in 9 patients. Adriani expressed the belief that use of the drug was more hazardous than the results justified.

Since 1944 we have employed "intocostrin" in 3 patients, all of whom died. After doses of 20 to 100 mg. these patients secured immediate relief of spasm, were able to move, void and defecate. Relief lasted, however, for only a brief period, ranging from twenty minutes to two hours. All 3 patients died in convulsive spasms. Hypersecretion was troublesome in all. Diplopia and dysphagia occurred in 2. In 1 case respiratory depression occurred three times, requiring use of oxygen by mask. One patient with severe laryngeal spasm not relieved by additional "intocostrin" required tracheotomy. He also had profound drops in blood pressure after "intocostrin" injections.

The following case is representative (fig. 1).

E. M., a 35 year old white man, was admitted to the hospital May 22, 1945, complaining of stiff neck, difficulty in opening his mouth and generalized muscle aching of three days' duration and of chronic osteomyelitis of the left leg of four years' duration. Physical examination revealed an acutely ill man in opisthotonus with trismus, stiff neck and back, abdominal rigidity and generalized muscle spasms. There was a chronic ulcer of the left lower leg. The patient was given antitoxin, penicillin, meperidine hydrochloride ("demerol" hydrochloride) and dextrose intravenously. An 80 mg. dose of "intocostrin" was administered three hours after admission. The patient relaxed immediately, but a second dose was required twenty minutes later. Two hours and fifteen minutes after the initial dose the patient had severe laryngeal spasm, and an emergency tracheotomy was performed. Over a period of twenty-four hours he received a total of 440 mg. of "intocostrin." After each dose of curare, blood pressure fell to shock levels. Injections of ephedrine and neostigmine produced only temporary improvement. An electrocardiogram taken twenty minutes after "intocostrin" was injected revealed only sinus

4. Wells, T. S.: Three Cases of Tetanus, in Which Woorara Was Used in the Treatment, Lancet **2**:562-564 (Dec. 3) 1859. Hoffmann, F. A.: Ein fall von tetanus traumaticus mit curare behandelt, Berl. klin. Wchnschr. October 1879, pp. 637-639.

5. Cole, L.: Tetanus Treated with Curare, Lancet **2**:475-477 (Sept. 1) 1934.

6. Mitchell, J. S.: Case of Tetanus Treated with Curarine, Lancet **1**:262-264 (Feb. 2) 1935.

7. West, R.: Intravenous Curarine in the Treatment of Tetanus, Lancet **1**: 12-16 (Jan. 4) 1936.

8. Cullen, S. C., and Quinn, C. S.: The Use of Curare in the Treatment of Tetanus: Case Report, Surgery **14**:256-260 (Aug.) 1943.

tachycardia. Spinal tap on admission yielded a clear fluid with 6 lymphocytes. The patient died thirty-six hours after admission. Autopsy revealed purulent meningitis which was attributed to reaction to the antitoxin. Culture of the leg ulcer yielded Clostridium tetani.

We concluded from our experience that "intocostrin" is of limited value in control of tetanic spasms because of its extremely short action, the danger of producing asphyxia by laryngeal paralysis or respiratory paralysis with hypersecretion and its tendency occasionally to produce profound drops in blood pressure.

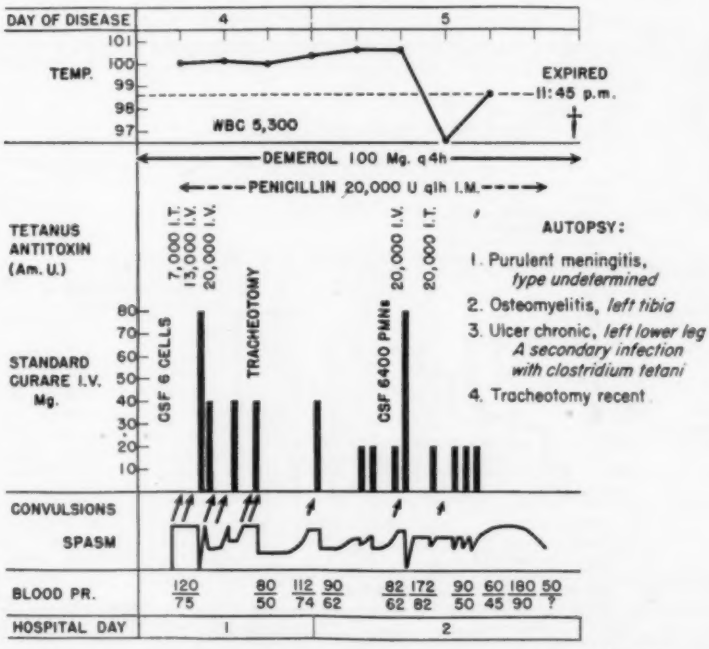


Fig. 1.—Graphic summary of data concerning patient E. M.

D-Tubocurarine in Wax and Oil.—Since June of 1947 we have treated 3 patients with d-tubocurarine in wax and oil [9] intramuscularly. Each cubic centimeter of this preparation contains 175 mg. of d-tubocurarine in 4.8 per cent wax in peanut oil. This drug produces a long-acting curare effect without many of the unpleasant side reactions of "intocostrin." Schlesinger [10] has given 1,500 injections of this preparation in amounts ranging from 0.4 to 2.5 cc. to 200 patients. The length of action in his series varied from twenty-four hours to one hundred and sixty-eight hours with longer action in the cases of less severe disease.

9. Provided by E. R. Squibb & Sons, New York.

10. Schlesinger, E. B.: Curare—A Review of Its Therapeutic Effects and Their Physiological Basis, Am. J. Med. **1**:518-530 (Nov.) 1946.

In the absence of a method for measuring blood levels of curare, it is necessary to gage dosage of d-tubocurarine in wax and oil by clinical observation. The dosage employed in our 3 cases ranged from 0.6 to 2.0 cc. daily with total d-tubocurarine dosages of 2,485 mg. in eleven days, 2,700 mg. in eighteen days and 3,570 mg. in fourteen days. There seemed to be no cumulative action in the doses given, and in 1 patient spasm tended to increase slightly before twenty-four hours had elapsed. We began treatment cautiously with 0.6 cc. and increased the dose daily until the patient was comfortably relaxed and free of spasms. The main-

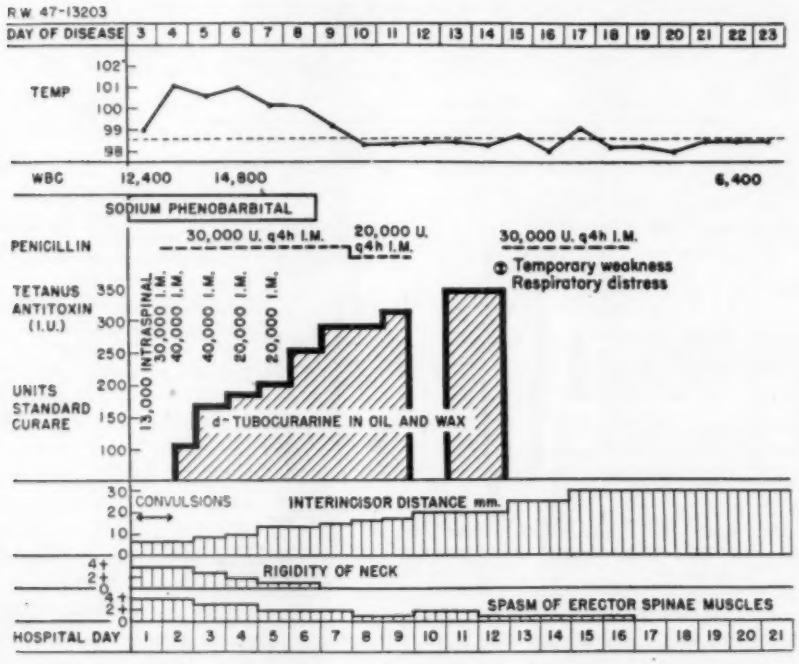


Fig. 2.—Graphic summary of data concerning patient R. W.

tenance dose varied between 1.25 cc. for an 11 year old boy and 2 cc. for an 80 Kg. man. Within two to three hours after the initial injection, 2 of the 3 patients showed decreased muscle spasm and increase in the interincisor distance. The third was more comfortable on the following day, although severe local tetanus in the right leg persisted. This patient, treated for eighteen days, did not have the infected focus removed. When maintenance doses were reached, the patients were able to eat, urinate and defecate and were not stimulated into spasm when they were examined. Stiffness of the back was the last sign to disappear. Electrocardiograms of these patients before, during and after treatment showed no significant changes. The systolic blood pres-

sure fell between 10 and 20 mm. but there was no notable change in the pulse rate.

Only 1 patient showed any toxic effect. This patient, while sitting on the bed pan, experienced difficulty in breathing with increased salivation and cyanosis, which was relieved by aspiration and oxygen within an hour. It was thought that he had inadvertently massaged the site of injection with release of a toxic amount of curare.

The following case is representative (fig. 2).

R. W., a 45 year old Negro man, was admitted to the hospital Sept. 28, 1947, complaining of generalized muscle stiffness of two days' duration, of difficulty in opening his mouth and of severe abdominal spasms of one day's duration. He had smashed his left ring finger three weeks before. Physical examination revealed an acutely ill man in opisthotonus with risus sardonicus, nuchal rigidity and abdominal spasm. The terminal phalanx of the left ring finger revealed the old crusted injury. He was treated immediately with antitoxin, penicillin and phenobarbital

TABLE 5.—*Treatment in Tetanus*

Preoperative	
1.	Tetanus antitoxin sensitivity tests—skin and conjunctival
2.	D-tubocurarine in wax and oil, 1 cc. intramuscularly
3.	Tetanus antitoxin, 60,000 units intravenously
4.	Tetanus antitoxin, 10,000 units locally
5.	Preoperative medication
Operative	
6.	General anesthesia
7.	Tetanus antitoxin 20,000 units intrathecally
8.	Debridement of wound
Postoperative	
9.	Sedation—chloral hydrate, paraldehyde, ether
10.	Tetanus antitoxin, 5,000 units daily for five to ten days
11.	D-tubocurarine in wax and oil intramuscularly daily to tolerance
12.	Penicillin, 50,000 units intramuscularly every three hours
13.	Maintain nutrition orally and parenterally
14.	Available at bedside—nasal oxygen, laryngoscope, endotracheal tube, aspirating apparatus

sodium, and the wounded was debrided. D-tubocurarine in wax and oil was given in increasing dosage, starting with 0.6 cc. the day following admission. The patient received a total of 2,485 mg. over a period of ten days. Response to the drug was gratifying; within three hours there was a lessening of abdominal spasms. With larger doses there was daily increase in interincisor measurement, with disappearance of the stiffness in abdominal and back muscles. On the eleventh day of treatment the drug was discontinued. Moderate stiffness of the back returned for a few days, but this was not troublesome. He was discharged twenty days after admission.

We concluded from these observations that in some instances d-tubocurarine in wax and oil can be given for periods up to eighteen days in sufficient dosage to control the convulsions and muscle spasm of tetanus without serious toxic effect.

Sedation.—All of the patients treated in this series received sedatives. Many were given four to six different hypnotics. None was completely satisfactory. The work of Firor, Lamont and Shumacker,[1a]

however, indicates that drugs which depress the respiratory center, especially the barbiturate derivatives and tribromoethanol solution ("avertin with amylene hydrate [solution]"), shorten the life of experimental animals with tetanus. The sedatives of choice are those which depress respiration least. Of these administration of chloral hydrate orally, paraldehyde orally or by rectum and ether in oil by rectum are preferable.

Analysis of the reviewed cases has aided us in formulation of a plan of treatment in tetanus designed to reduce the rate of mortality (table 5).

COMMENT

The plan of treatment is divided into three phases: preoperative, operative and postoperative. The patient on admission is immediately given a cutaneous test and conjunctival test with tetanus antitoxin diluted 1:100. If sensitivity is present, desensitization is attempted or "despeciated" antitoxin is given if available. If a wound can be found, 50,000 units of antitoxin is given intravenously and 10,000 units locally around the wound. If no wound is found, the entire contents of three 20,000 unit vials is given intravenously.

As soon as the sensitivity test is given, 1 cc. of d-tubocurarine in wax and oil is administered intramuscularly. For immediate control of convulsions, "intocostrin" may be given intravenously, but we prefer to remove the patient to the operating room at once for ether anesthesia. In the operating room, with the patient anesthetized, 20,000 units of tetanus antitoxin is injected intrathecally and the wound debrided.

Postoperatively the patient is returned to a darkened private room with a special nurse. Available at the bedside are nasal oxygen, a laryngoscope, an endotracheal tube and aspirating apparatus. Appropriate medication for rest is ordered. Penicillin is given every three hours to prevent infections of the respiratory tract and for its action on infected wounds. Penicillin, although it is said to have a bacteriostatic effect on Cl. tetani, has no apparent effect on the toxin produced and no proved clinical effect in the treatment of generalized tetanus.[11]

Five thousand units of tetanus antitoxin is given daily to neutralize any additional toxin that may be absorbed. This is continued for five days if the infected focus has been removed, longer if the focus cannot be found.

D-tubocurarine in wax and oil is given intramuscularly daily according to the clinical response of the patient. Relief of spasm can be obtained without the production of laryngeal or diphragmatic paral-

11. Altmeier, W. A.: Penicillin in Tetanus, J. A. M. A. **130**:67-72 (Jan. 12) 1946.

ysis. Patients who receive this medication must, in the present state of our knowledge, be watched constantly by experienced personnel in order that any evidence of curare toxicity may be coped with immediately.

SUMMARY

Eighty-two cases of tetanus from three Detroit hospitals are reviewed. Special attention is given to recent cases in which "intocostrin" and d-tubocurarine in wax and oil were used in treatment. From this experience it is concluded that while "intocostrin" (contains raw crude curare) is unsatisfactory in routine treatment of tetanus, d-tubocurarine in wax and oil is effective in controlling tetanic muscle spasms without undue hazard and may be a significant advance in the treatment of this disease. A plan of treatment is formulated.

DISCUSSION

DR. KELLOGG SPEED, Chicago: Possibly one statement might be challenged; namely, the statement that the wound should be debrided. Was it the authors' intention, after postoperative tetanus, such as after hemorrhoidectomy, herniorrhaphy or amputation, to find indication for opening up and debriding an operative wound? Would they reamputate, or would they debride those wounds postoperatively?

DR. HOMER M. SMATHERS, Detroit: We had only 1 case of postoperative tetanus in our series, in which a herniorrhaphy had been done. Tetanus was recognized on the sixth postoperative day. The patient was given the usual antitoxin, and the wound was reopened and debrided down to the peritoneum. The patient made a good recovery. It is our feeling that the deformity or morbidity of a debrided operative wound is of minor concern when compared to the known high mortality rate of the disease. We would, therefore, debride an amputation stump and in a hemorrhoidectomy would attempt to establish an aerobic medium by drainage and a loose pack of activated zinc peroxide.

DR. GROVER C. PENBERTHY, Detroit: It has been my privilege to review this series of cases which Dr. Smathers and his co-workers have presented, and because time did not permit them to relate some of the history as regards curare I thought it would be of interest to inject this into the discussion. Curare was used in the treatment of tetanus in 1859. Sir Thomas Spencer Wells used a preparation in treatment in 3 postoperative cases of tetanus. Use of this drug was then forgotten until the 1930's, when Cole, Mitchell and West all treated tetanus with curare. Cullen and Quinn reported 1 case in 1943 and mentioned treatment in 3 others. Adriani supervised the use of curare in 9 cases of tetanus, but expressed the belief that the drug was more hazardous than results justified.

At the Children's Hospital of Michigan in Detroit we have treated 30 patients with tetanus over a fifteen year period. There were 16 deaths, a mortality rate of 53 per cent. It is of considerable interest that 1 patient with tetanus neonatorum was seen and the disease diagnosed in 1940 by Dr. James Wilson, then Director of Pediatrics at this hospital. This patient, a Mexican male child, was delivered in the home by a physician. On the twelfth day of life he refused to nurse and was taken to the hospital. On the thirteenth day he exhibited spasms, opisthotonus and trismus. He was given 40,000 units of antitoxin intramuscularly; 250 mg. doses of

tribromoethanol solution ("avertin" with amylene hydrate [solution]) were given by rectum seven times. On the second hospital day he was given 1 mg. of curare intravenously. He relaxed immediately, but twenty minutes later required more curare. Dosage was entirely dependent on clinical observation. On the third and fourth day 10 mg. doses were given, but the patient died during convulsions. Autopsy revealed pulmonary edema and suppurative omphalitis. Previous culture of the umbilical wound had been negative for Clostridium tetani. Dr. Smathers, Dr. Johnston and Dr. Weed are to be commended for their interest in making this extensive study.

DR. WILLIAM A. ALTEMEIER, Cincinnati: The treatment of established tetanus is still a very real problem, and the experience of the authors coincides with ours at Cincinnati General Hospital in many respects. The mortality rate in proved cases with generalized convulsions remains between 50 and 60 per cent in series reported from most of the general hospitals throughout the country. The most important prognostic sign is the length of the incubation period, the mortality rate decreasing as the duration of the incubation period increases. In 33 cases studied at the Cincinnati General and neighboring hospitals during the past three years, we have been impressed by the fact that the majority of deaths occurred as a direct result of acute respiratory arrest. We were also impressed by the minor and relatively trivial injuries which led to the development of tetanus.

Experimental and clinical evidence seems to indicate that no amount of antitoxin will reverse the course of the disease once a fatal dose of toxin becomes fixed in the central nervous system. The data suggest that a secondary toxin is formed in the central nervous system as a result of the fixation of the primary toxin and that the secondary toxin is not neutralized by tetanus antitoxin.

The use of d-tubocurarine in oil should be a helpful addition to our therapeutic armamentarium, but I do not believe the mortality rate will be appreciably altered until we have found some method of direct attack on the toxin after its fixation in the central nervous system or on the theoretical secondary toxin. We have used curare in treatment in 4 of our cases without any obvious effect on the mortality rate.

We believe that penicillin will not effect the course of tetanus *per se*, since the disease is a manifestation of the body to toxin already fixed in the central nervous system and since our studies have shown no power of penicillin to neutralize or alter tetanus toxin. Nevertheless, it may have a beneficial effect in preventing or attenuating associated infections, such as hypostatic pneumonia or pyogenic wound infections.

HEMORRHAGIC CYST OF THE MESENTERY OF THE ILEUM

HARRY A. OBERHELMAN, M.D.
AND
JOHN B. CONDON, M.D.
CHICAGO

BENEVIENI in 1507 described the first mesenteric cyst, which he observed at autopsy. During the subsequent years scattered reports appeared in the literature, of which an excellent review was made by Warfield [1] in 1932. He estimated that some five hundred mesenteric cysts had been reported. He made no attempt to classify them.

The first definite classification of these cysts was attempted by Dowd [2] in 1900, who proposed three groups, namely, embryonic, hydatid and cystic malignant disease. Most investigators have stated the opinion that mesenteric cysts are embryonic in origin. Various classifications have been offered by such authors as Snyder,[3] Nye and Wilkins,[4] Roller,[5] Hueper,[6] Peterson,[7] Carter [8] and Lahey and Eckerson.[9] Of these various authors, the classification presented by Peterson (table) seems complete and satisfactory.

Higgins and Lloyd [10] stated that true mesenteric cysts occur in or near the mesentery and possess a distinctive lining membrane. They excluded malignant, dermoid and parasitic cysts and those cysts arising from any normally placed retroperitoneal organ. This view is shared

Read at the fifth annual meeting of the Central Surgical Association, Chicago, Feb. 19, 1948.

1. Warfield, J. O., Jr.: A Study of Mesenteric Cysts, Ann. Surg. **96**:329, 1932.
2. Dowd, C. N.: Mesenteric Cysts, Ann. Surg. **32**:515, 1900.
3. Snyder, J. W.: Mesenteric Cysts, South. Surgeon **8**:240, 1939.
4. Nye, G. C., and Wilkins, A. L.: Mesenteric Cysts, Ann. Surg. **54**:115, 1911.
5. Roller, C. S.: Mesenteric Cysts, Surg., Gynec. & Obst. **60**:1128, 1935.
6. Hueper, W. C.: Mesenteric Enterocystoma, J. Lab. & Clin. Med. **12**:427, 1926.
7. Peterson, E. W.: Mesenteric and Omental Cysts, Ann. Surg. **96**:340, 1932; Cysts of the Mesentery, ibid. **112**:80, 1940.
8. Carter, R. M.: Cysts of the Mesentery, Surg., Gynec. & Obst. **33**:544, 1921.
9. Lahey, F. H., and Eckerson, E. B.: Retroperitoneal Cysts, Ann. Surg. **100**: 231, 1934.
10. Higgins, T. T., and Lloyd, E. I.: Mesenteric Cysts, Brit. J. Surg. **12**:95, 1924.

by Loeb,[11] who regarded a true mesenteric cyst as one occurring between the two leaves of the mesentery or beneath the intestinal serosa and having a distinctive lining membrane. Peterson classified cysts of the mesentery which occur without a distinctive lining membrane as pseudocysts. The singular feature about any discussion of mesenteric cysts is that little or no mention is made of hemorrhagic cyst as a separate pathologic entity.

The term "sanguinous" is used in designating one type of embryonic cyst with hemorrhage. Also, the term "hematoma of the mesentery" has been employed to designate hemorrhagic cysts in known trauma to the mesentery. Furthermore, the term "apoplexy" of the mesentery has been used in describing a hematoma of spontaneous origin. It is a well

Peterson's Classification of Mesenteric Cysts

I. Embryonic
  A. Arising from embryonic remnants and sequestrations may be:
    (a) Serous
    (b) Chylous
    (c) Sanguinous
    (d) Dermoid
  B. Cysts of intestinal origin, arising as a result of:
    (a) Sequestration of the bowel
    (b) Diverticula of the concave side of the bowel, thus reaching an intramesenteric position
  C. Cysts arising from urogenital organs
    (a) Germinal epithelium
    (b) Ovary
    (c) Wolffian body
    (d) Müllerian duct

II. Pseudocysts
  A. Infective origin
    (a) Hydatid cysts
    (b) Degenerated tuberculous nodes
  B. Cystic malignant disease

known fact that secondary hemorrhage may occur in any mesenteric cyst, regardless of the cause; however, when this does occur there is usually some anatomic evidence, whether gross or microscopic, or both, still present in the wall which will establish the identity of the type of cyst. When such evidence is not available to establish the identity of the cyst wall, then one is dealing with a cyst of doubtful origin, giving cause for considerable speculation and debate. In such circumstances the use of the term "pseudocyst" may be warranted.

We wish to present this case report for the following reasons:

1. There is still much to be said to clarify the confusion existing in the literature on the subject of hemorrhagic cysts of the mesentery. This applies particularly to their origin and also to their clinical and pathologic classification.

11. Loeb, M. J.: Mesenteric Cysts: Review of Literature, Genesis and Classification, with Report of One Case, New York State J. Med. **41**:1564, 1941.

2. Most of the reports in the literature dealing with mesenteric cysts make little or no mention of hemorrhagic cysts of the mesentery, whether true cysts or pseudocysts. In a reasonably complete survey of the available literature we have found only one like condition, reported by Gazmuri, Gonzalez and Lepe.[12]

REPORT OF A CASE

M. H., a white man aged 40, who weighed 145 pounds (about 66 Kg.) and was a cosmetic manufacturer, was admitted to Mercy Hospital July 3, 1947, complaining of a movable mass in the abdomen. The patient stated that two and a half months previously he first noted a dull aching nonradiating pain in the lower part of the abdomen, especially noticeable about thirty minutes after a meal. The larger the meal, the severer his pain would be. At times the pain was noted in the left upper quadrant. He was seen by a physician, who prescribed ulcer management, with no apparent improvement. Two weeks later the patient first noted a freely movable mass in his abdomen when he lay down. The presence of the mass was later confirmed by his physician, and the patient was referred to us for observation and for further treatment.

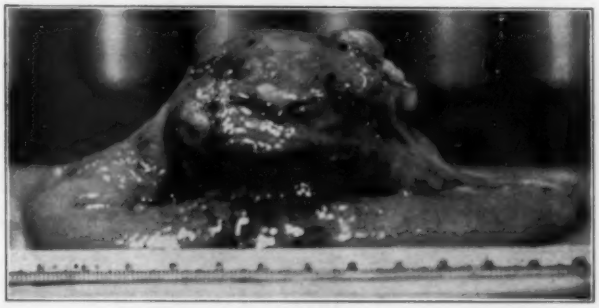


Fig. 1.—Hemorrhagic cyst with the attached segment of ileum.

The past history was noncontributory except for a nephropexy on the right side eight years previously. The noteworthy observations on physical examination were confined to the abdomen, which was flat, without visible masses or pulsations. On palpation there was a spherical movable tender mass, 9 to 10 cm. in diameter in the left upper quadrant. The liver, kidneys and spleen were not palpable. Laboratory reports showed red blood cells 4,000,000, white blood cells 7,400, hemoglobin 14 Gm. (90.9 per cent), normal urine (voided specimen) and prothrombin time 89 per cent. Chemical observations of the blood were as follows: nonprotein nitrogen 38 mg., sugar 80 mg. per hundred cubic centimeters and serum proteins 5.05 Gm. On July 5, under general anesthesia, with "pentothal sodium" N. N. R. (sodium 5-ethyl-5-[1-methylbutyl] barbiturate) induction and cyclopropane and oxygen-gas mixture. surgical exploration was performed through a left rectus incision. A deep red spherical mass, approximately 7 to 8 cm. in diameter, was seen between the leaves of the mesentery of the ileum and extending from its attachment to the bowel proximally for three quarters of the length of the mesentery. As a result

12. Gazmuri, R.; Gonzales, J., and Lepe, A.: Hematic Cyst of Mesentery, Rev. méd. de Chile **72**:709, 1944.

of organizing reaction at the periphery of the mass, the peritoneum over it was covered with a fibrinous exudate, to which the greater omentum was adherent. Removal of the cyst alone was obviously impossible without destroying the blood supply of the adjacent ileum; hence the cyst and the corresponding segment of the ileum (27 cm.) were resected *in toto*. The bowel was repaired by an open end to end anastomosis and the mesenteric defect closed. One pint (about 473 cc.) of blood was given during the operation.

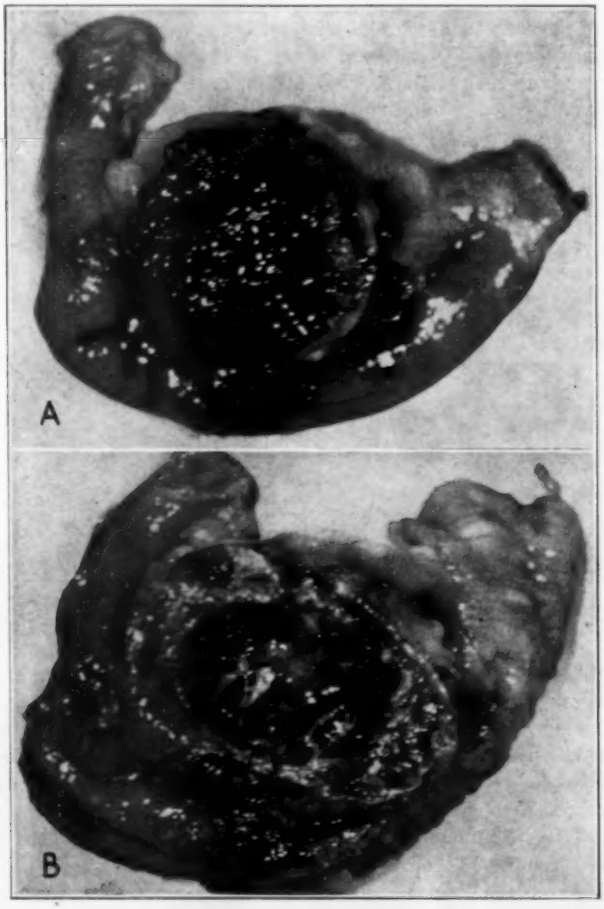


Fig. 2.—*A*, hemorrhagic cyst showing the dark blood clot occupying the cavity of the cyst. *B*, hemorrhagic cyst after evacuation of the blood clot seen in *A*.

Pathologic Observations.—The cystic mass was ensheathed between the leaves of mesentery of the ileum and was tensely distended (fig. 1). On section the cystic space was seen to be completely occupied by a rather recent reddish blue blood clot (fig. 2*A*), and about the periphery of the fresh blood the cystic wall was lined with an old organizing reddish gray clot (fig. 2*B*). The cyst wall varied in thickness from 2 to 4 mm. The inner cyst wall was composed of interlacing bands of upraised and trabecularly arranged septums. The cyst, however, was unilocular, with no communicating intestinal sinus tract. In addition, a triangular segment of omental fat presented two identical oval small cystic structures, 1.1 and

0.6 cm. in diameter. These cysts, on section, were seen to contain altered chocolate brown syrup-like blood and were lined by smooth glistening deep gray tissue.

On microscopic section, the wall of these cysts was observed to be made up of fibrocollagenous tissue with scattered areas of granulation tissue, representing beginning organization of the periphery of the blood clot (fig. 3). There was no evidence of malignant growth. A few foamy finely reticulated macrophages were present, as well as hemosiderin carrying macrophages and hemosiderin deposits. The cyst contents were made up entirely of old laked and decolorized blood. A lining membrane was nowhere apparent.

CONCLUSIONS

On the basis of gross and microscopic studies, it seems apparent that this hemorrhagic cyst of the mesentery was not of the usual varieties

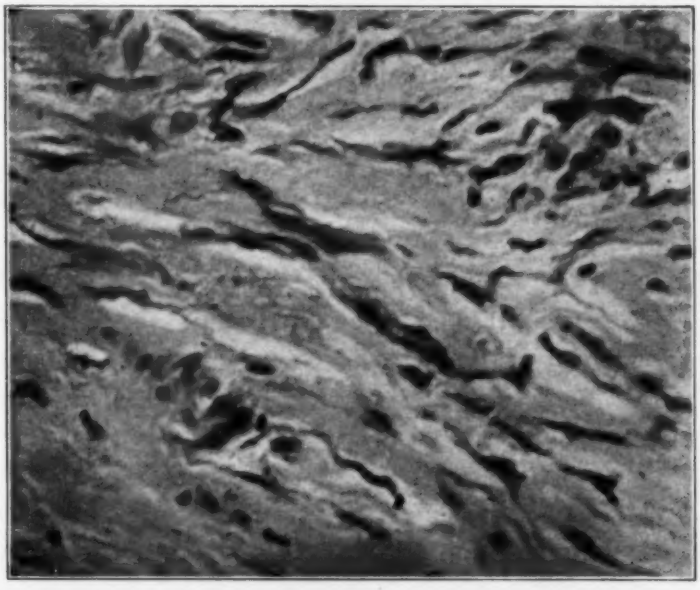


Fig. 3.—Photomicrograph of the cyst wall, showing that it lacked a lining membrane.

of cystic mesenteric tumors, because a distinctive lining membrane was nowhere in evidence. However, it is conceivable, but not likely, that repeated secondary hemorrhages, with subsequent organization of the periphery of the blood clot, may eventually destroy any such lining membrane completely. On the other hand, degenerative lymph nodes in the mesentery may become surrounded by a fibrous wall enclosing a cystic mass into which secondary hemorrhage may occur, but since the lymph nodes elsewhere in the mesentery were grossly unaltered, this, too, is not likely to be the causative factor. Finally, trauma to the abdomen would appear to be the most likely causative factor, in spite of a denial by the patient. Yet, it is common knowledge that blunt

violence, whether direct or indirect, need not be sufficiently severe for the patient to remember having sustained it and might still result in abdominal hemorrhage. Therefore, since the hemorrhagic cyst in this report had all the features of an organizing encapsulated hematoma and particularly since one would hardly suspect arteriosclerotic disease at the age of 40, trauma, in our opinion, appears to be the most likely causative factor. Furthermore, since this cyst was devoid of any distinctive lining membrane, it may therefore be classified as a pseudocyst. As to treatment, it is recommended that a cyst impinging on the junction of the bowel and the mesentery, unless small, should be removed with the corresponding segment of intestine, because of the danger of circulatory interference to such a segment.

30 North Michigan Avenue.

SURGICAL REMOVAL OF UNSUSPECTED MEDIASTINAL LYMPHOBLASTOMAS

Report of Four Cases and a Review of the Literature

BYRON H. EVANS, M.D.
AND
CAMERON HAIGHT, M.D.
ANN ARBOR, MICH.

SINGLE unilateral circumscribed mediastinal tumors of lymphoblastic origin are infrequently encountered. Their roentgenologic appearance closely simulates that of mediastinal tumors of the dermoid or teratomatous type. The correct preoperative diagnosis may be difficult to establish, as the lymphoblastic nature of the tumor may not be suspected. Furthermore, even when it is suspected, the response to a test dose of radiation occasionally is so limited that this method of differential diagnosis may prove to be fallacious.

The purpose of this study is to report 4 cases of lymphoblastic mediastinal tumors which have been removed at the University of Michigan Hospital during the past ten years. In 3 of the cases the correct diagnosis was not suspected before operation. In the fourth case, the diagnosis of a lymphoblastic tumor was considered; a test dose of radiation was advised but was not given as had been planned. In each instance the tumor was thought to be a benign lesion before operation and at the time of its removal. It was not until the pathologic examination was completed that the diagnosis of lymphoblastoma became apparent. Histologic examination of the resected lesions showed two to be Hodgkin's disease and two to be lymphosarcoma. One of the patients with Hodgkin's disease died of recurrence seven and three-fourths years after operation. The other patients are alive and apparently free from recurrence five and one-third, four and one-third and two and one-half years, respectively, after operation.

REPORT OF CASES

CASE 1.—P. G., a 38 year old housewife, was admitted to the University Hospital on June 8, 1938, with the complaint of severe cough of eleven years' duration. She had noted blood-streaked sputum, wheezing, paroxysms of cough and dyspnea on several occasions during the previous year. A roentgenogram of the chest in

From the Department of Surgery, University of Michigan Medical School, Ann Arbor.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

April 1938 revealed an abnormal density in the right hilus suggestive of a mediastinal tumor. She did not appear acutely or chronically ill, and the results of the general physical examination were essentially normal.

Roentgen examination of the chest (fig. 1) revealed a rounded mediastinal mass projecting into the right hemithorax and measuring approximately 7 cm. in its greatest diameter. It was seen to lie in the anterior mediastinum on the lateral projection. The diaphragm moved normally on fluoroscopy, and the mass exhibited transmitted rather than expansile pulsations, as was substantiated by kymographic studies. The impression was that the mass most probably represented a dermoid cyst.

Laboratory examination revealed normal urine, and the Kahn reaction of the blood was negative. The red blood cell count was 4,170,000, hemoglobin 11.6 Gm., or 76 per cent, and the white blood cell count 11,600. The differential count revealed 70.5 per cent polymorphonuclear leukocytes, 3.5 per cent eosinophils, 8 per cent

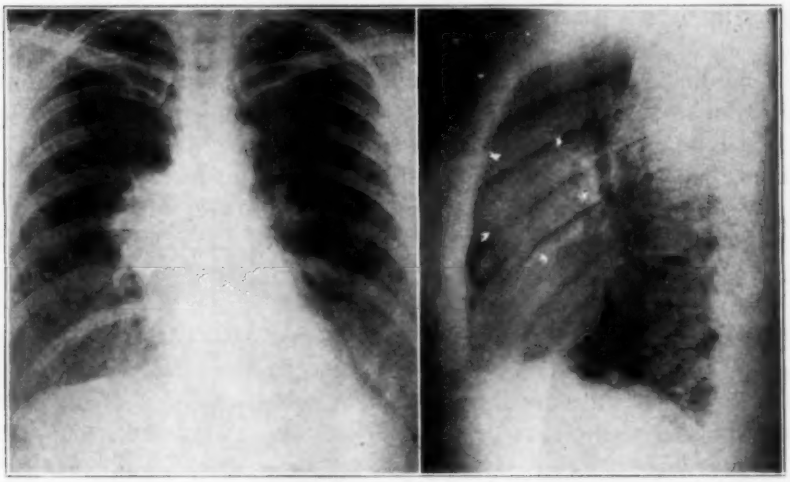


Fig. 1 (case 1).—Roentgenograms, June 8, 1938, show a rounded anterior mediastinal mass projecting into the right hemithorax.

small lymphocytes, 10.5 per cent large lymphocytes, 7 per cent monocytes and 0.5 per cent lymphoblasts. The blood picture was interpreted by Dr. F. H. Bethell as suggestive of lymphoblastoma.

A bronchogram on June 14 showed mild compression of the right stem bronchus, as if by an anterior extrinsic mass. Bronchoscopic examination revealed an essentially normal tracheobronchial tree. A test dose of radiation was not given, as the lesion was believed to be a benign tumor, probably a dermoid cyst.

Exploratory thoracotomy was performed by Dr. John Alexander on July 1. The pleural cavity was entered through a right posterolateral incision, and an oval tumor of the size of one's fist was visualized anterior to the inferior portion of the superior vena cava. The tumor was stony hard in consistency and projected into the right hemithorax. The inferior portion of the upper lobe was loosely adherent to the tumor on its superior and lateral surfaces. The mediastinal pleura was densely adherent to the mass, but by alternate sharp and blunt dissection a satisfactory cleavage plane was established and the tumor was completely removed. The pedicle was at the superior pole of the mass. It was the surgeon's impression

that the lesion was a dermoid cyst. The mediastinal pleura was loosely closed with silk, and the chest was closed without drainage. The postoperative period was uneventful, and the patient was discharged on July 21.

The pathologic diagnosis was a lymphoblastoma of the Hodgkin's type, with extensive fibrosis (Dr. R. C. Wanstrom) (fig. 2).

The patient returned one month later and received 400 r measured in air to each of an anterior and posterior mediastinal port. Roentgenograms at this time showed no evidence of mediastinal enlargement.

The patient was not seen again until fifteen months after operation, when she returned with the complaint of difficulty in swallowing and midsternal discomfort.

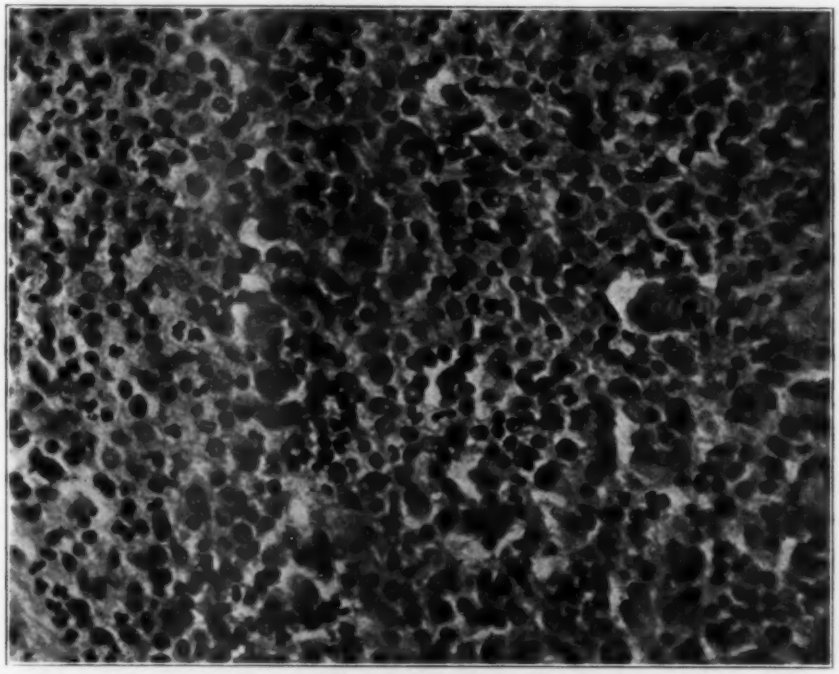


Fig. 2 (case 1).—Photomicrograph shows Dorothy Reed giant cells, eosinophils, endothelial proliferation and loss of follicular architecture characteristic of Hodgkin's disease.

Roentgen examination following the ingestion of barium sulfate revealed esophageal compression by a superior mediastinal mass above the level of the original tumor (fig. 3*A*). The symptoms were relieved by radiation consisting of 1600 r directed to the mediastinum (fig. 3*B*). During the next six and one-half years the patient had periods of exacerbations, with remissions brought about by roentgen therapy, until her death on March 29, 1946, of generalized Hodgkin's disease. Autopsy was not done.

Case 2.—S. B., a 31 year old meat cutter, was admitted on Sept. 15, 1942, with the complaint of frequent colds during the preceding four winters. During the last year he had noted small amounts of thick yellowish sputum without odor or blood streaking. He complained of mild pain in the right side of the chest and

slight dyspnea on exertion. There had been no weight loss. The past history was not contributory and the results of the physical examination were essentially normal. The patient appeared to be in good health.

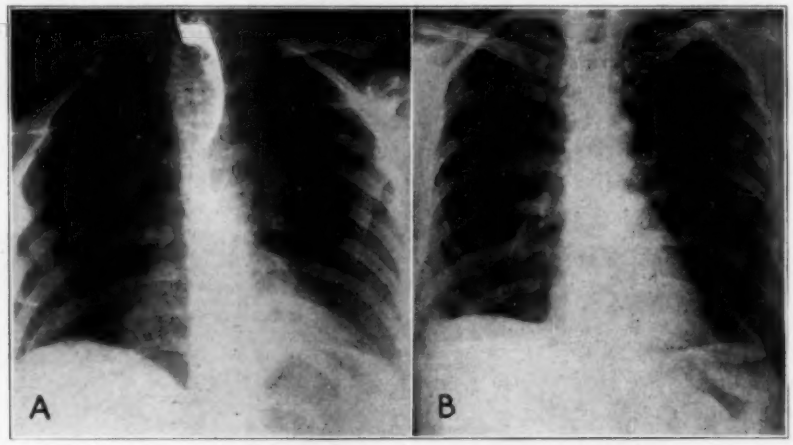


Fig 3 (case 1).—*A*, roentgenogram, Sept. 28, 1939, fifteen months after operation shows a mediastinal mass above the original location of the tumor. *B*, roentgenogram, Aug. 25, 1944, shows no evidence of mediastinal enlargement following radiation.

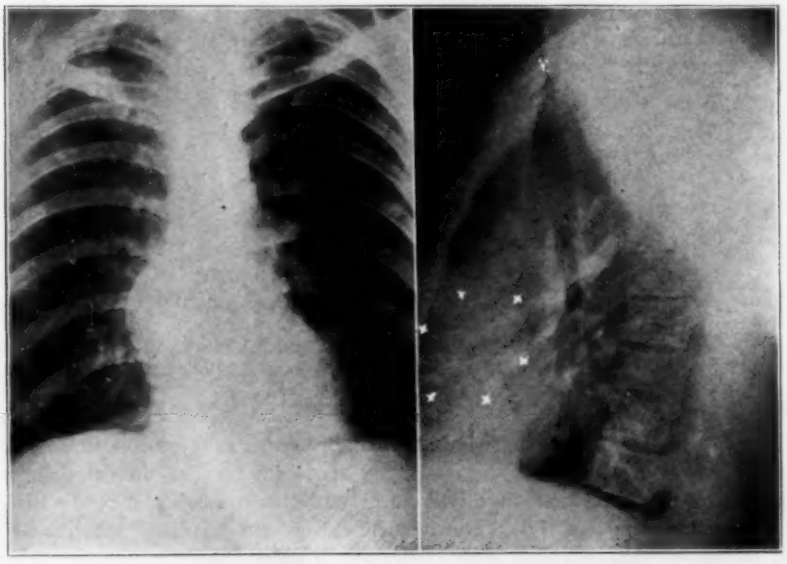


Fig. 4 (case 2).—Roentgenograms, Sept. 15, 1942, showing anterior mediastinal density projecting into the right hemithorax. The fine line of increased density along the lateral margin of the tumor represents calcification within its capsule.

Roentgen examination of the chest revealed a dense sharply demarcated oval mass in the anterior inferior mediastinum, projecting into the right hemithorax (fig. 4). The periphery of the mass was outlined by a thin layer of calcium.

although no calcified structures were visualized within the substance of the tumor (fig. 5). The impression was that the density represented a dermoid cyst with calcification of its wall.

Laboratory examination revealed normal urine, and the Kahn reaction of the blood was negative. The red blood cell count was 4,340,000 and the hemoglobin 14 Gm., or 95 per cent. The red blood cells on smear were normal. The white blood cells numbered 5,400, and the differential count revealed 70 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes, 3 per cent eosinophils and 4 per cent monocytes.

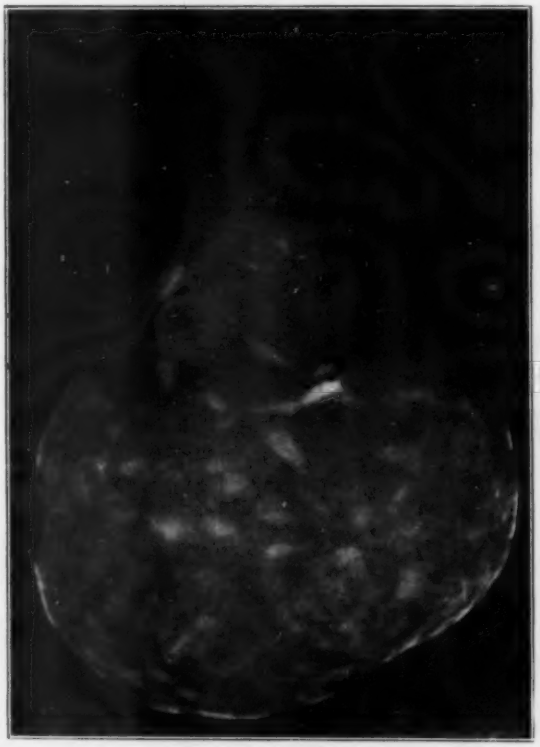


Fig. 5 (case 2).—A roentgenogram of the specimen showing widespread calcification of the capsule.

Operation was performed by one of us (C. H.) on Oct. 13, 1942. A firm hard rounded tumor mass was seen to arise from the mediastinum anterior to the right pulmonary hilus. It was partially adherent to the adjacent surface of the upper lobe of the lung. The upper lobe was readily freed from the tumor. After incision of the thin mediastinal pleura overlying the tumor, an excellent cleavage plane was found. A small projection of the tumor extended upward and across the mediastinum. The mass was readily removed after its blood supply had been ligated at the superior pole. The chest was closed without drainage. The postoperative course was uneventful aside from the accumulation of fluid that necessitated several thoracenteses.

The tumor measured 6.5 by 6 by 4 cm. Pathologic examination by Dr. C. V. Weller revealed a lymphosarcoma partially replacing the thymus (fig. 6). There were large areas of necrosis. The capsule showed plaques of fibrocalcified material attached to the surface of the tumor, and numerous cholesterol clefts were observed in a homogeneous matrix beneath layers of fibrous connective tissue.

The patient was observed at intervals after operation. Roentgenograms of the chest, including the most recent ones, of Feb. 17, 1948, showed no evidence of recurrence of the mediastinal lymphosarcoma (fig. 7). Examination showed no evidence of recurrence or of new disease. At the time of writing the patient was working regularly and had no symptoms referable to his chest.

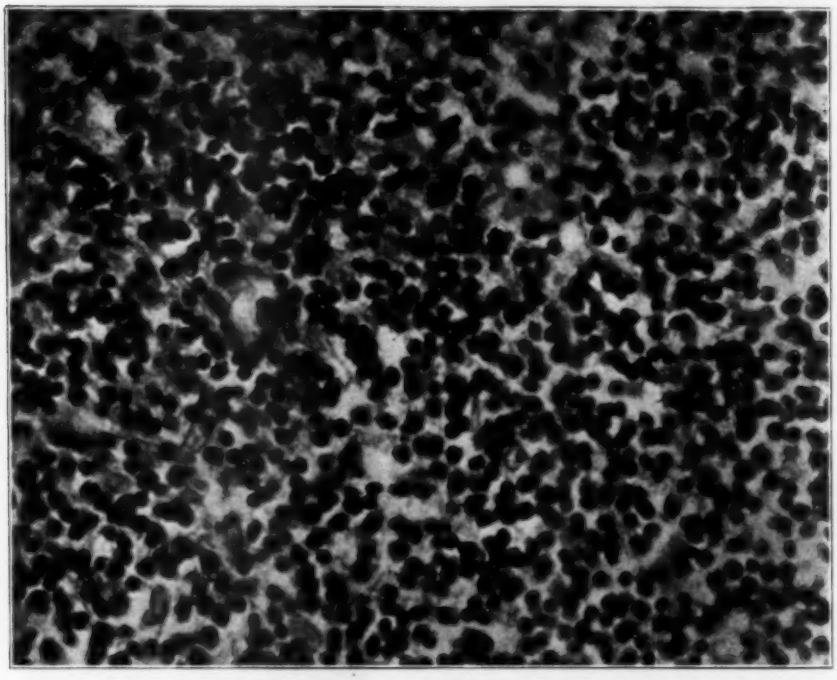


Fig. 6 (case 2).—Photomicrograph showing uniform neoplastic cells of the lymphocytic type characteristic of lymphosarcoma.

CASE 3.—M. D., a 33 year old steel worker, was admitted on Oct. 10, 1943. In July he had been told at an Army Induction Center that he had an intrathoracic tumor on the left and that he should seek medical care. He was entirely without symptoms, and the results of the physical examination were normal.

Roentgen examination of the chest revealed a smoothly rounded anterior mediastinal mass which projected into the left hemithorax (fig. 8*A*). The impression was that the mass represented a benign tumor, probably a dermoid cyst.

Examination of the blood showed the hemoglobin to be 100 per cent and the white blood cell count 7,750. A differential count of the white blood cells was not done. The urine was normal and the Kahn reaction to the blood was negative.

Operation was performed by Dr. John Alexander on October 11. When the left pleural cavity was entered, a rounded and almost circular anterior mediastinal mass, with irregular elevations on its surface, was seen projecting into the left

hemithorax. The mediastinal pedicle was broad, measuring approximately 7 cm. in diameter. Later in the operation the lowermost portion of the tumor was dissected free, leaving a true pedicle of approximately 2 cm. in diameter arising from

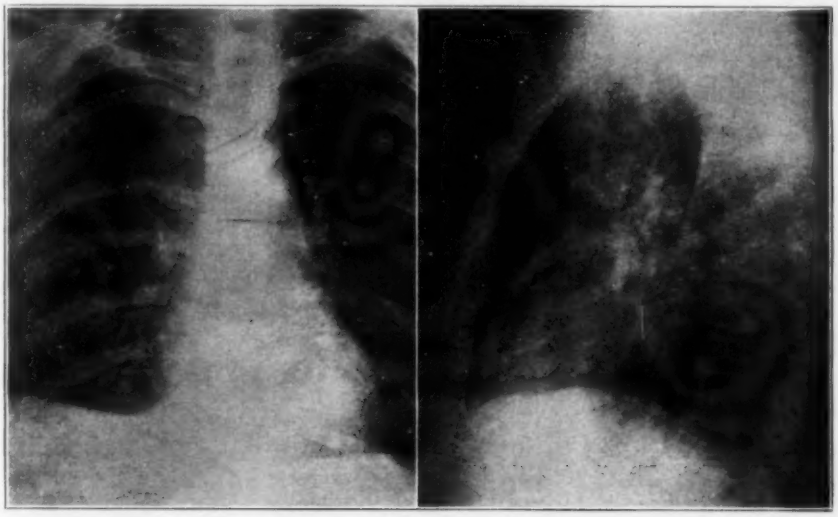


Fig. 7 (case 2).—Roentgenograms, Feb. 17, 1948, five and one-third years after operation show no recurrence.

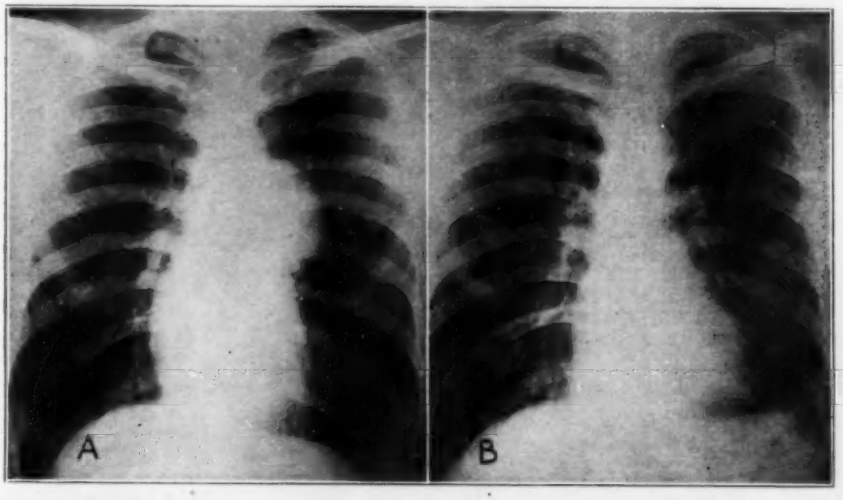


Fig. 8 (case 3).—*A*, roentgenogram, Aug. 30, 1943, shows a rounded mediastinal density projecting into the left hemithorax. *B*, roentgenogram, July 11, 1947, three and three-quarters years after operation shows no recurrence. (Roentgenograms by Dr. Paul C. Bovard, Taretum, Pa.).

the mediastinum over the left innominate vein anterior to the phrenic nerve and 3 cm. superior to the aortic arch. The tumor was completely removed without difficulty. The chest was closed without drainage. The postoperative course was

uneventful aside from the aspiration of serosanguineous fluid from the pleural space on several occasions.

The pathologic examination showed the lesion to be a rounded mass measuring approximately 8 cm. in its greatest diameter. Microscopic examination by Dr. R. C. Wanstrom revealed large masses of lymphosarcoma which had infiltrated dense connective tissue (fig. 9). The surface of the mass was covered by a layer of dense connective tissue which appeared to form a capsule.

The patient received postoperative radiation consisting of 1200 r measured in air to each of an anterior and posterior port. The radiation was given on the advice of Dr. I. Lampe because of the nature of the lesion, although the tumor had apparently been completely removed grossly.

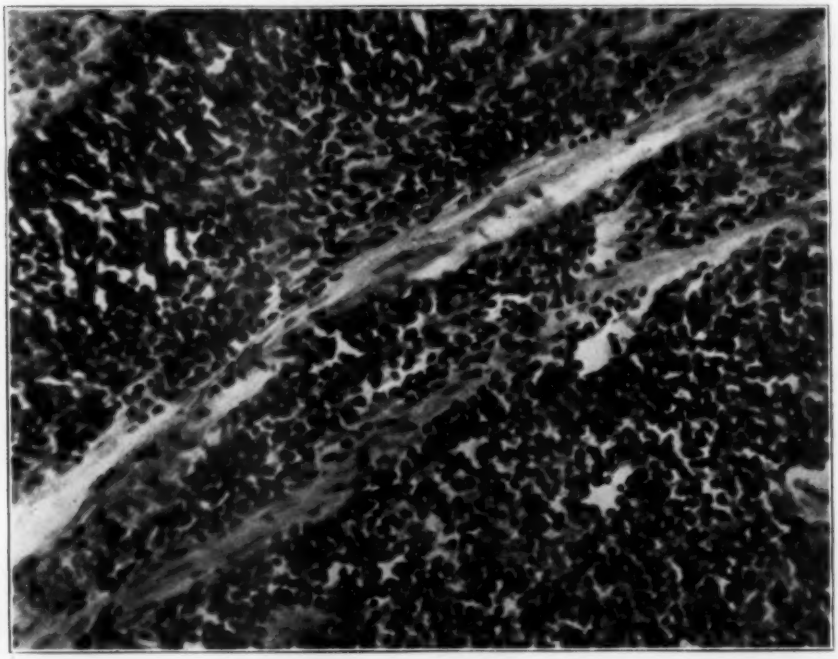


Fig. 9 (case 3).—Photomicrograph showing large masses of lymphosarcoma infiltrating dense connective tissue.

Roentgenograms of the chest were made at intervals after operation. All examinations, including the last one, on July 11, 1947, revealed no evidence of recurrence (fig. 8 *B*). The patient was apparently well and asymptomatic at the last report on Feb. 17, 1948.

Case 4.—J. N., a 23 year old police clerk, was admitted on Sept. 19, 1942, with the complaint of fatigue of five years' duration. He attributed the symptom to the presence of a mediastinal mass which had been noted on an employment roentgenogram five years previously. There was slight exertional dyspnea which was believed to be caused by moderate obesity, but there was no cough, hemoptysis or thoracic pain. Roentgen examination of the chest revealed an anterior mediastinal tumor projecting into the left hemithorax (fig. 10 *A*). The patient declined surgical treatment and did not return until two and one-half years later. The

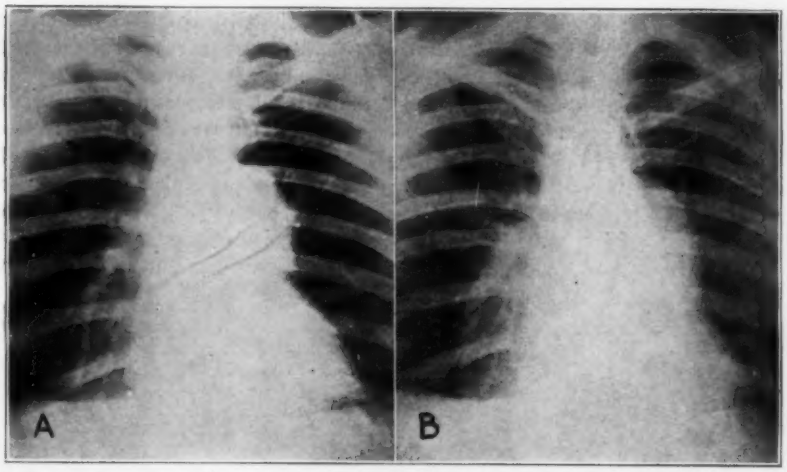


Fig. 10 (case 4).—*A*, roentgenogram, Sept. 19, 1942, shows a mediastinal density overlying the arch of the aorta and projecting into the left hemithorax. *B*, Roentgenogram, June 15, 1945, shows a definite increase in the size of the mass in comparison with roentgenogram *A*, made on Sept. 19, 1942.

Fig. 11 (case 4).—Roentgenogram, June 15, 1945, shows the anterior position of the mediastinal mass.

dyspnea on exertion had increased slightly, and two small hemoptyses had occurred two weeks previously. He had contracted syphilis and gonorrhea two years previous to this admission. Treatment had apparently been adequate. The Kahn reaction of the blood was negative, and results of laboratory studies of the urine and blood were not remarkable. The red blood cell count was 5,700,000, the hemoglobin 15.7 Gm., or 100 per cent, and the white blood cell count 12,900. The differential count revealed 71 per cent polymorphonuclear leukocytes, 1 per cent basophils, 3 per cent eosinophils, 9 per cent large lymphocytes, 10 per cent small lymphocytes and 6 per cent monocytes. The blood picture was interpreted by Dr. F. H. Bethell as showing high normal blood values with no abnormal blood cells

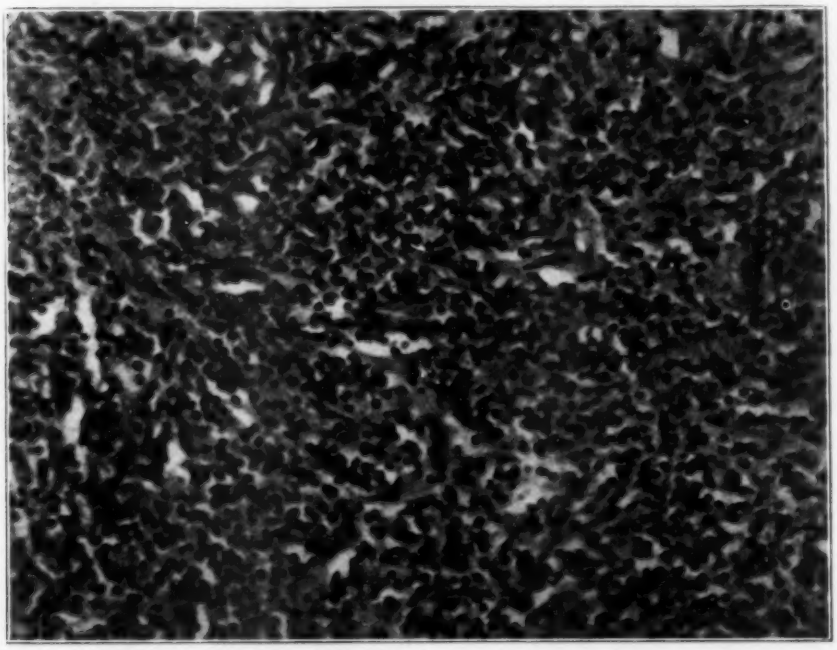


Fig. 12 (case 4).—Photomicrograph shows many formed vessels, with occasional eosinophils, giant cells, reticuloendothelial elements and considerable fibrous tissue. Sclerosing type of Hodgkin's disease.

seen. The results of the Ascheim Zondek test were negative and bronchoscopy, on June 25, 1945, revealed no abnormalities.

Roentgen examination of the chest on June 15, 1945, (fig. 10 *B*) revealed a moderate increase in the size of the mediastinal density since the examination of September 1942. Kymographic studies showed slight pulsations of the left lateral margin of the tumor mass which were presumed to be transmitted rather than expansile. It was believed that the lesion was a dermoid cyst, although aortic aneurysm and lymphoblastoma were considered.

The patient was readmitted on Aug. 27, 1945, and a thoracotomy was performed by one of us (C. H.) on September 2. A firm dense lobulated tumor, measuring 10 by 8 by 6 cm., arose from the mediastinum immediately above and anterior to the hilus of the left lung. The superior border of the tumor extended to the upper level of the aortic arch. The phrenic nerve was identified along the

mesial border of the tumor. An excellent cleavage plane was readily established about the mass, and it was removed completely. The postoperative course was entirely uneventful, and the patient was discharged from the hospital on September 14.

The examination of the specimen by Dr. R. C. Wanstrom revealed a mass of lymph nodes showing partial preservation of the follicular architecture in areas, while elsewhere it was entirely lost. There were many formed vessels with eosinophils and reticuloendothelial elements. The diagnosis was sclerosing Hodgkin's disease (fig. 12).

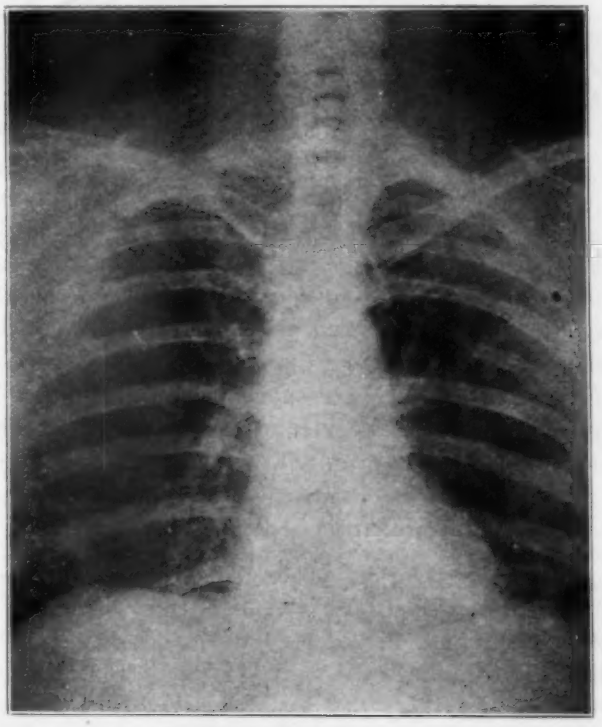


Fig. 13 (case 4).—Roentgenogram, Feb. 16, 1948, two and one-half years after operation shows no evidence of recurrence.

The patient was not given postoperative radiation. His progress has been followed at frequent intervals by roentgen examination of the chest. Physical examination and roentgenograms (fig. 13) on Feb. 16, 1948, showed no evidence of recurrence or new disease. At the time of writing the patient was apparently well and working full time.

COMMENT

It is difficult to ascertain the incidence of isolated mediastinal lymphoblastomas. It is well know that mediastinal tumors are relatively uncommon. Zanca and Herple,[1] in an analysis of 100,000 consecutive

1. Zanca, P., and Herpel, F. K.: A Statistical Analysis of 100,000 Examinations of the Chest by the Photoroentgen Method, Radiology **43**:122-128 (Aug.) 1944.

roentgenograms of the chest at an Army Induction Center, were able to find only two mediastinal tumors, an incidence of 0.02 per thousand. Such a low rate might in part be explained by the screening of the selectees by the local examining boards. In 10,(` roentgen examinations of the chest in a general hospital, Scatchard and Duszynski [2] found 2 cases of unspecified mediastinal tumors and 1 of Hodgkin's disease. Those cases in which the initial lesions of Hodgkin's disease and lymphosarcoma produce mediastinal enlargement with a roentgen appearance characteristic of a benign lesion are apparently uncommon. Although Jackson and Parker [3] in a review of 174 cases of Hodgkin's disease reported 90 cases, or 52 per cent, with hilar or mediastinal nodes, it is noteworthy that in only 1 case was there evidence during life of an intrathoracic mass without coincident or antecedent peripheral lymphadenopathy.

The preoperative differentiation between a benign tumor and a lymphoblastic mediastinal lesion can be aided by the response of the malignant tumor to a test dose of radiation. Evans and Leucutia,[4] Haagensen,[5] Pfahler,[6] Arons,[7] Reynolds and Leucutia [8] and Robbins,[9] as well as others, have stressed the diagnostic importance of a test dose of radiation. It has been shown by Friedman [10] that many of the malignant mediastinal tumors of lymphoblastic origin respond to dosages of 750 r measured in air, directed to the mediastinum, while others will require as much as 1500 r to produce any change in size. This response to a test dose of radiation may be dramatic with the disappearance of the mediastinal shadow in three to four weeks.

---

2. Scatchard, G. N., and Duszynski, D. O.: Routine Chest Roentgenograms of Hospital Admissions, Dis. of Chest **12**:312-320 (July-Aug.) 1947.

3. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease: VII. Treatment and Prognosis, New England J. Med. **234**:103-110 (Jan. 24) 1946.

4. Evans, W. A., and Leucutia, L.: Deep Roentgen-Ray Exposure as an Aid in the Differential Diagnosis of Mediastinal Tumors, J. A. M. A. **85**:1215-1219 (Oct. 17) 1925.

5. Haagensen, C. D.: The Differential Diagnosis of Primary Neoplasms of the Mediastinum, Am. J. Cancer **16**:723-782 (July) 1932.

6. Pfahler, G. E.: Roentgen Diagnosis of Mediastinal Tumors and Their Differentiation, Am. J. Roentgenol. **31**:458-469 (April) 1934.

7. Arons, I.: Mediastinal Tumors and Malignant Lymphoma, Radiology **26**: 605-621 (May) 1936.

8. Reynolds, L., and Leucutia, T.: The Value of the Roentgen Therapeutic Test Dose in Differential Diagnosis of Mediastinal Tumors, Am. J. Roentgenol. **48**:440-466 (Oct.) 1942.

9. Robbins, L. L.: The Roentgenologic Features of Mediastinal Tumors, Radiology **43**:115-121 (Aug.) 1944.

10. Friedman, M., cited by Blades.[14]

Harrington,[11] Heuer,[12] Alexander,[13] Blades[14] and others have emphasized that if there is no change in the mediastinal density following a test dose of radiation surgical exploration should be undertaken. Prolonged radiation of benign lesions beyond that of a test dose is unwise, in that it does not prevent further growth and does not prevent malignant changes. Furthermore, it may make surgical excision more hazardous and difficult because of increased vascularity and adhesions.

A review of the literature reveals 6 cases of mediastinal lymphoblastoma in which apparently complete removal was accomplished (table). In the collected cases, as well as in the cases presented in this article, operation was undertaken on the assumption that the lesion was not lymphoblastic in origin.

Summary of Data in Cases of Mediastinal Lymphoblastoma with Surgical Removal

Case	Author	Date	Location	Diagnosis	Result	Follow-Up
1	Muller	1937	Anterior	Hodgkin's disease	Died of empyema	2 mo.
2	Leriche	1937	Posterior	Hodgkin's disease	Died of operation	.....
3	Monod and his co-workers	1946	Anterior	Hodgkin's disease	Apparently well	6 mo.
4	Blades (case 1).....	1946	?	Hodgkin's disease	Apparently well	9 mo.
5	Blades (case 2).....	1946	Posterior	Hodgkin's disease	Apparently well	8 mo.
6	Blades (case 3).....	1946	?	Hodgkin's disease	?	?
7	Evans and Haight (case 1)	1948	Anterior	Hodgkin's disease	Died of Hodgkin's disease	7¾ yr.
8	Evans and Haight (case 2)	1948	Anterior	Lympho-sarcoma	Apparently well	5½ yr.
9	Evans and Haight (case 3)	1948	Anterior	Lympho-sarcoma	Apparently well	4¼ yr.
10	Evans and Haight (case 4)	1948	Anterior	Hodgkin's disease	Apparently well	2½ yr.

Muller's[15] patient was a 17 year old girl who had had a roentgenogram of the chest three years previously because of a positive reaction to tuberculin. The roentgenogram revealed a left mediastinal

11. Harrington, S. W.: Surgical Treatment of Mediastinal Tumors, Ann. Surg. **96**:843-856 (Nov.) 1932.

12. Heuer, G. J.: Surgical Treatment of Tumors of the Mediastinum, Ann. Surg. **113**:357-363 (March) 1941.

13. Alexander, J.: Observations on Intrathoracic Neoplasms, Ann. Surg. **114**: 734-752 (Oct.) 1941.

14. Blades, B.: Mediastinal Tumors: Report of Cases Treated at Army Thoracic Surgery Centers in the United States, Ann. Surg. **123**:749-765 (May) 1946.

15. Muller, G. P.: Mediastinal Tumor Caused by Hodgkin's Disease, Ann. Surg. **105**:177-182 (Feb.) 1937.

mass, which was interpreted as enlarged hilar lymph nodes. Treatment consisted of bed rest for one year, but the lesion enlarged slightly during this time. An unspecified test dose of radiation was then given to the mediastinum, without response of the lesion, and a diagnosis of benign tumor was tentatively made. During the following two years the lesion showed progressive enlargement. Three years after the appearance of the lesion, the patient was operated on and the tumor was completely removed. The diagnosis of Hodgkin's disease was established on examination of the specimen. The patient died two months after operation as a result of empyema and pneumonia. At autopsy no residual disease of the lymphatic system was discovered.

Leriche's [16] patient was a 43 year old man with a unilateral discrete mediastinal mass projecting to the right. The preoperative diagnosis was dermoid cyst. The tumor was removed with considerable difficulty and bleeding, and the patient died soon after operation. The microscopic diagnosis was *lymphogranulomatose maligne* (Hodgkin's disease).

Monod, Bariéty, Lesobre and Choubrac [17] reported the case of a young woman in whom a mediastinal tumor was discovered as a result of a roentgenogram of the chest. The patient received radiation consisting of 2500 r directed at the mediastinum, with only slight response of the lesion. The mass slowly enlarged during the following two years, and operation was advised. The preoperative diagnosis was a dermoid cyst. The lesion was completely removed, and the patient made an uneventful recovery. The pathologic examination revealed Hodgkin's disease in which fibrous tissue predominated. Radiation consisting of 1500 r was given three months after operation. No further follow-up was reported.

In Blades' [14] series of one hundred and nine collected mediastinal tumors, fourteen malignant tumors were found; four were due to Hodgkin's disease and two to lymphosarcoma. Removal of the lesion was possible in 3 of the cases of Hodgkin's disease, but not in the remaining case of Hodgkin's disease or in the cases of lymphosarcoma. In 1 of the 3 cases with removal, operation was performed by Paulson; the tumor had invaded the upper lobe of the lung and it was necessary to perform an upper lobe lobectomy when the neoplasm was removed. The progress of this patient was not mentioned. In

16. Leriche, R.: Tumeur du médiastin postérieur diagnostiquée kyste dermoid; ablation, mort rapide, examen histologique lymphogranulomatose maligne, Lyon chir. **34**:168-171 (March-April) 1937.

17. Monod, R.; Bariéty, M.; Lesobre, R., and Choubrac, P.: Lymphogranulomatose maligne à détérmination thoracique simulant une tumeur bénigne du médiastin antérieur: Hippocratisme digital; Diagnostic histologique après exérèse, Bull. et mém. Soc. méd. de hôp. de Paris **62**:18-23 (Jan. 11) 1946.

another of the cases, in which Blades operated, the lesion was situated in the right posterior mediastinum. The tumor presented a lobulated appearance and was excised. Many palpable lymph nodes were noted near the pulmonary hilus. The patient received postoperative radiation therapy, and there was no evidence of recurrence on roentgenologic examination eight months after operation. In the third case with removal, operation was performed by Grow. Details of the case were not mentioned, but the patient had been under observation for approximately nine months with no evidence of recurrence of the tumor. Radiation therapy was withheld pending the development of signs of recurrence.

A preoperative test dose of radiation without significant response of the lesion was given in 2 of the 10 cases mentioned, i. e., the cases of Muller and of Monod and his co-workers. The pathologic diagnosis in both of these cases revealed Hodgkin's disease with considerable fibrous tissue, presumably the sclerosing type of Hodgkin's disease.

Insufficient time has elapsed in the cases with removal of mediastinal lymphoblastomas to allow an evaluation regarding the length of survival. In Muller's and Leriche's cases, death followed operation. The period of postoperative observation in the other previously reported cases is less than one year and is too short to be of significance. Patient 1 in this series died of generalized Hodgkin's disease seven and three-quarters years after operation. Although the patients in cases 2, 3 and 4 in this series were apparently well and without evidence of recurrence five and one-third, four and one-third and two and one-half years after operation, respectively, the late result in these cases cannot be foretold.

Occasional long survivals with absence of symptoms after the removal of isolated cervical Hodgkin's disease are reported. Jackson and Parker mentioned 2 patients without symptoms for twenty-four and thirty-four years, respectively. In 1 of their cases a recurrence that led to the patient's death from widespread Hodgkin's disease first appeared twenty-four years after surgical excision. Pund and Stelling [18] reported 3 cases of apparently arrested lymphosarcoma, 2 of which resulted from surgical removal of isolated peripheral nodes, with radiation postoperatively and a survival of eight and eleven years, respectively. Their third patient was suspected of having a gastric carcinoma. The lesion was considered to be irremovable at operation, and biopsy of a serosal nodule disclosed the presence of lymphosarcoma. The patient refused postoperative radiation, but gradually improved and was alive and well six years later.

18. Pund, E. R., and Stelling, F. H.: Lymphosarcoma: Report of Three Apparently Cured Cases, Am. J. Surg. **52**:50-54 (April) 1941.

Sugarbaker and Craver [19] and Stout [20] stated that the best prognosis is obtained in those patients in whom the disease is limited to one area at the time treatment is begun. This opinion was expressed irrespective of whether treatment is by radiation, by surgical intervention or by both. Furthermore, Stout [20] and Jackson and Parker expressed the belief that if operation is to be the primary treatment it is advisable to employ postoperative radiation therapy. In this connection Sugarbaker and Craver reported 25 cases with excision followed by radiation, with six, or 24 per cent, five year symptom-free survivals; in a comparable series of patients treated by radiation alone 16 per cent survived five years, and only half of these were symptom free.

In the cases with removal of mediastinal lymphoblastomas, postoperative radiation was used in the case of Monod and his co-workers, in 1 of Blades' cases and in 2 of the cases in this series (cases 1 and 3). In case 2 and case 4 in this series, radiation was withheld on the advice of the radiologist that it should be reserved for the treatment of a recurrence or of new disease. It is paradoxic that the only patient in this series who is known to have had a recurrence is one (case 1 in this series) with Hodgkin's disease who received prophylactic postoperative radiation. The dosage employed in this case was small, being 400 r to an anterior port and a similar dose to a posterior port. After the development of new lesions of Hodgkin's disease fifteen months after operation, the lesions showed prompt, although only temporary, response to a therapeutic dose of radiation.

Because of the possibility of late recurrence, a long survival without symptoms cannot be regarded as a cure. Craver [21] recently expressed doubt that anyone is able to produce an authenticated case of cure in Hodgkin's disease or lymphosarcoma at the present time. It is preferable to regard symptom-free survival as an apparent arrest of the disease rather than as a cure. This point of view is particularly applicable if lymphoblastic diseases are of a multicentric origin. If this theory is true, all surgical and roentgen treatment must be considered to be of a palliative nature. If the origin is from a unicentric focus, however, as appeared to be true in Muller's case, a cure by extirpation of the localized lesion is theoretically possible. Craver suggested that evidence for such a possibility is accumulating.

---

19. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: Study of One Hundred and Ninety-Six Cases with Biopsy, J. A. M. A. **115**:17-23 (July 6) 1940; **115**:112-117 (July 13) 1940.

20. Stout, A. P.: Is Lymphosarcoma Curable? J. A. M. A. **118**:968-970 (March 21) 1942.

21. Craver, L. F.: Lymphomas and Leukemias: The Value of Early Diagnosis and Treatment, J. A. M. A. **136**:244-249 (Jan. 24) 1948.

It is not the purpose of this paper to express a preference for surgical removal over treatment by radiation. A test dose of radiation should be given in all cases of mediastinal tumors in which a reasonable possibility of lymphoblastoma exists. This plan is particularly indicated in instances of anterior mediastinal tumors. If the radiation produces a decided regression, surgical intervention should not be considered. Should the lesion be radioresistant or only mildly radiosensitive and should it present an isolated circumscribed appearance suggesting that it can be removed, the possibility of operative measures should be considered, in the hope of obtaining prolonged freedom from symptoms or conceivably a cure. The period of observation following surgical removal in the cases to date is too brief and the number of cases too limited to allow an evaluation of this method. Although one can scarcely expect a cure in these cases, the problem merits further study until it can be determined whether improvement sufficient to warrant the operation or possibly a cure can be obtained.

SUMMARY

Four cases of mediastinal lymphoblastomas, which simulated benign lesions, are reported. Histologic examination of the neoplasms showed the disease in 2 to be Hodgkin's disease and in 2 to be lymphosarcoma. One of the patients with Hodgkin's disease died of recurrence seven and three-quarter years after operation. The remaining 3 patients were alive and apparently well, five and one-third to two and one-half years following operation. Six previously reported cases of mediastinal Hodgkin's disease with apparent complete removal are discussed.

DISCUSSION

DR. LEON J. LEAHY, Buffalo: I would like to ask Dr. Evans and Dr. Haight whether it is their practice to make a biopsy of a suspected lymphoblastoma of the mediastinum before instituting roentgen therapy? It has been my custom to give a test dose of about 600 r. After ten days, anteroposterior and lateral roentgenograms are made to determine whether or not there has been any decrease in the size of the lesion and in this way determine whether or not it is radiosensitive.

DR. CAMERON HAIGHT, Ann Arbor, Mich.: In the cases which Dr. Evans and I have reported operation was done under the erroneous assumption that the lesions were dermoid cysts. The possibility of a lymphoblastoma was not considered in the first 3 cases, because the lesions were apparently slowly growing ones having the isolated unilateral appearance of benign tumors by roentgen examination and were without evidences of involvement of the peripheral lymph nodes. In the fourth case, the possibility of a lymphoblastic lesion was considered; a test dose of radiation was advised but was not given. The lesson to be derived is that even when a mediastinal lesion has the characteristic appearance of a dermoid cyst, a test of radiation should be given to be certain that it is not lymphoblastic in nature.

Although it was not our intention to remove apparently isolated lymphoblastomas, it is of interest to note that the concept of excision of peripheral

isolated lymphoblastic lesions is not new. It was suggested by Yates and Bunting in 1917, by Lerche in 1929 and by Eggers in 1937. More recently Sugarbaker and Craver have mentioned that the course of the disease was more favorable if isolated lesions could be removed as a preliminary to radiation of the area than if treated by radiation alone. Further experiences with mediastinal lymphoblastomas will be needed to determine whether surgical removal will aid the prognosis of those lesions which do not show a typical response to a test dose of radiation. The most that can be said at present is that the patients whom we have reported were improved, rather than harmed, by operation.

The subject of pulmonary cysts has been ably presented by Drs. McGrath and Magnussen. As they and Dr. Curreri have mentioned, pulmonary cysts may stimulate other lesions, such as empyema and pulmonary abscess. An important point in the differential diagnosis is that the symptoms in cases of pulmonary cysts are usually less severe than would be anticipated from the roentgen appearance of the lesion. If pulmonary cysts are producing toxic symptoms and copious expectoration, it is often safer to drain them externally as the first step and to postpone their removal until a later date, after the symptoms have subsided. By the routine practice of biopsy of pleura or lung, when drainage is done in cases of apparent empyema and pulmonary abscess respectively, the presence of a previously unsuspected epithelial lined cyst can occasionally be recognized.

FAT EMBOLISM

A Diagnostic Enigma

FRANK R. DENMAN, M.D.
AND
LOGAN GRAGG, M.D.
LOUISVILLE, KY.

IN THE past few years the problem of thromboembolic disease as an important complication of surgical treatment has been repeatedly emphasized. In contrast fat embolism, though equally common, is seldom mentioned and is less often recognized clinically or pathologically, primarily because of failure to regard it as a possibility.

Reports vary as to the incidence of fat embolism.* Whereas clinicians feel that it is rare, positive evidence has been reported at autopsy in slightly less than one half of the bodies examined.[1] In a recent series of 1,000 battle casualties, Wilson and Salisbury[2] reported 8 cases with 6 deaths. Darrach[3] reported 2 cases in a series of 12,000 cases of fracture and Groendahl[4] stated that fat embolism is the cause of death in only 1 per cent of the deaths following fractures. On the other hand, Vance[1b] in a series of 246 routine autopsies found some degree of fat embolism in 44.3 per cent, and in 14 cases (5.7 per cent) the condition was of sufficient severity as to constitute an adequate cause for death. Likewise, Wright[1c] reported 100 autopsies, in which he found fat in the pulmonary capillaries in 52 cases; of these, the condition in 4 was significantly severe. In this regard, deTakats[5] stated that fat embolism occurs more frequently than any other type.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

From the Departments of Surgery and Pathology, University of Louisville School of Medicine and the Louisville General Hospital, Louisville, Ky. Dr. Denman is Instructor in Surgery and Dr. Gragg Instructor in Pathology, University of Louisville School of Medicine.

1. (*a*) Lehman, E. P., and McNattin, R. F.: Fat Embolism, Arch. Surg. **17**: 179, 1928. (*b*) Vance, B. M.: The Significance of Fat Embolism, ibid. **23**:426, 1931. (*c*) Wright, R. B.: Fat Embolism, Am. J. Surg. **96**:75, 1932.

2. Wilson, J. V., and Salisbury, G. W.: Fat Embolism in War Surgery, Brit. J. Surg. **31**:384, 1932-44.

3. Darrach, W., in discussion on Harris, Perret and MacLachlin.[15]

4. Groendahl, N. B., cited by Scuderi.[17e]

5. deTakats, G.; Beck, W. G., and Fenn, K. F.: Pulmonary Embolism, Surgery **6**:339, 1939.

In our series of 99 autopsies, selected at random, there were 7 cases (7.07 per cent) in which the condition was of sufficient severity as to be considered the primary cause of death. In an additional 24 (24.2 per cent) fat emboli were present but were scarce and were not judged sufficient to account for death. By comparison, in a recent autopsy study of 4,070 postoperative deaths, McCartney [6] found 471 cases (11.5 per cent) in which thrombotic embolism was present and 216 (5.3 per cent) in which pulmonary embolism was considered the cause of death. Certainly, then, the incidence of fat embolism parallels that of thrombotic embolism and thus deserves equal consideration (table 1).

The causation and pathogenesis are still obscure. There is usually an association with trauma to adipose tissue, particularly that in the osseous system, and the disease in the majority of cases follows frac-

TABLE 1.—*Incidence of Severe Fat Embolism and Thrombotic Embolism*

Severe Fat Embolism	
Clinical observation	
Authors	Percentage
Wilson and Salisbury	0.8
Darrach	0.016
Observation at autopsy	
Authors	
Vance	5
Wright	4
Denman and Gragg	7
Thrombotic Embolism	
Observation at autopsy	
Author	
McCartney	5

tures and orthopedic operations; however, in a number of cases the condition has been reported to follow injury to the subcutaneous tissue and fatty viscera. Less often fat embolism has been found in association with chemical poisons, osteomyelitis, eclampsia, diabetes mellitus, pancreatitis, tuberculosis and other conditions (see figure).[7] The significance of these associations is controversial. Usually the degree of embolization is slight and is of no clinical or pathologic significance. On the other hand, severe embolization is a reliable indication of trauma and, in the absence of another explanation, constitutes a competent cause of death.[8]

6. McCartney, J. S.: Post-Operative Pulmonary Embolism, Surgery **17**:191, 1945.

7. Vance.[1b] Warthin, A. S.: Traumatic Lipemia and Fatty Embolism, Internat. Clin. **4**:71, 1913.

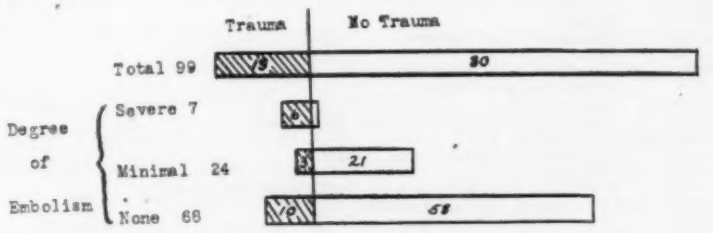
8. (*a*) Gauss, H.: The Pathology of Fat Embolism, Arch. Surg. **9**:593, 1924. (*b*) Vance.[1b]

In this series of 99 autopsies of adults 19 patients died after trauma. Of these 6 (5, fractures, 1, burn) had severe fat embolism, 3 slight and 10 none. Of the remaining 80 patients who died without trauma only 1 had severe fat embolism, 21 had a slight degree of embolization and 58 had none (figure).

Thus in 7 autopsies fat embolism was so severe as to be judged the primary or heavily contributing cause of death. In the 5 cases of fracture no other cause of death was apparent. In the case of burn probably other physiochemical pathologic condition was active. In the 1 case in which there had been no trauma there were found severe pyelonephritis and cystitis, sufficient alone to cause death but associated with severe pulmonary edema and massive fat embolism (table 2).

In 24 other autopsies a few fat emboli were demonstrated, but all of these had apparently completely unrelated fatal disease (table 3).

It is said that fat embolism is produced by physical trauma when



Graphic Analysis of 99 autopsies.

TABLE 2.—*Cases of Severe Disease*

Autopsy Number	Causative Association
A46-141	Fractured femur and cerebral hemorrhage
A46-272	Fractured femur
A46-284	Fractured femur
A46-236	Fractured humerus and ilium
A46-285	Fractured clavicle and subcutaneous injury
A46-252	Second and third degree burns involving 70 per cent of the body surface
A46-256	Pyelonephritis and cystitis pulmonary edema

three conditions are met.[8a] These are: first, an injury to adipose tissue producing disruption of membranes and stroma liberating liquid fat into the injured areas; second, rupture and patency of veins, and, third, increase in local pressure. All of these conditions are effective in bone trauma, for here venous collapse does not occur, the vein walls being supported in the haversian canals. Furthermore, local pressure increases rapidly subsequent to edema and hemorrhage and liberated bone marrow fat enters the open veins. In trauma to subcutaneous tissue or to fatty viscera the mechanism of entry is not

clear, for increase in local pressure should result in collapse of all open veins and thus prohibit entry of fat into the circulation. In cases in which there has been no trauma the mechanism is even more obscure. It has been suggested that some chemical change occurs in the blood or in the blood fat which causes a demulsification and coalescence of the chylomicrons into globules of sufficient size to obstruct capillaries. Lehman and Moore [9] were able to produce fat emboli in dogs by first producing alimentary lipemia and then giving the dogs ether. They believed that the ether acted as a demulsifying agent. Apparently the physical state of blood fat is of more importance than its amount, for, as Warren [10] reiterated, high degrees of lipemia

TABLE 3.—*Fat Emboli Present but Scarce*

Autopsy Number	Causative Association
A46-5	Dislocation vertebra (no fracture)
A46-13	Pyoderma; multiple metastatic abscesses; pulmonary embolism
A46-19	Subdural hematoma
A46-22	Coronary occlusion
A46-28	Empyema
A46-31	Poison?
A46-54	Rheumatic heart disease
A46-66	Aortic aneurysm
A46-94	Arteriosclerotic heart disease
A46-98	Hirschsprung's disease
A46-109	Meningitis
A46-121	Carcinoma of the colon with obstruction
A46-209	Tuberculosis
A46-145	Coronary occlusion; renal infarct
A46-216	Pneumonia
A46-218	Squamous cell carcinoma of cervix with metastasis
A46-219	Dehydration and malnutrition
A46-257	Toxemia of pregnancy
A46-262	Myocardial infarct
A46-265	Skull fracture
A46-280	Intestinal obstruction
A46-282	Cerebral arteriosclerosis; ulcers of sigmoid of unknown origin
A46-243	Poison?
A46-248	Tuberculosis

exist in diabetic coma, and yet the occurrence of fat embolism is exceedingly rare.

There is no one mechanism which is definite in every case. On the contrary it is probable that several factors are involved, including mobilization of fat from injured areas and a change in the physical state of the blood fat due to alterations in body metabolism and chemistry by either trauma or disease.

It is well to remember that fat embolism is not a true embolism in the sense of a permanent occlusion of a vessel, but rather a slowing of blood flow through a capillary bed while oil droplets become elongated and are slowly forced from the arterial to the venous side of the circulation. Thus mobilized fat enters the regional veins and

9. Lehman, E. P., and Moore, R. M.: Fat Embolism Including Experimental Production without Trauma, Arch. Surg. **14**:621, 1927.

10. Warren, S.: Fat Embolism, Am. J. Path. **22**:69, 1946.

is carried through the right side of the heart into the lungs, where droplets become lodged in the capillaries. After a variable period of time some of the emboli are forced through the lung and enter the systemic circulation again to become lodged in the capillary bed of all the organs. The maximum number of emboli that is compatible with life is unknown, and the balance rests on the rate and degree of embolization versus the ability of the organism for elimination.

Elimination of fat emboli from the vascular system has been estimated to require from eight to fourteen days.[11] There are four processes which may occur: first, by escape from renal glomeruli into the urine; second, excretion by the liver into the bile; third, phagocytosis, and, fourth, emulsification by the mechanical action of the blood current perhaps aided to some extent by the saponifying action of blood lipase.[8]

Pathologic diagnosis is made by the demonstration of fat droplets in capillaries. Warren [10] has shown that the presence of fat may be suspected when one finds vacuoles in the glomerular tufts or in the parenchyma of the lung in routine sections. It is essential to determine the degree of embolization in order to evaluate its significance. A severe degree may be said to exist if fat droplets are seen in the majority of capillaries in every low power field, and embolization may be considered significant if there is involvement in at least every other field. Occasionally, the fat droplets are accompanied with fragments of bone marrow which, of course, are readily recognized in routine sections. Warren [10] found 3 such cases. Lindsay and Moon [11a] reported 4 and referred to another.[12] In only 1 of our autopsies was this observation recorded.

The most outstanding gross observation is pulmonary edema combined with signs of anoxia. Occasionally the blood in the pulmonary artery may appear oily.[10] In 1 of our cases multiple minute acute gastric ulcers were seen. Frozen sections stained with scarlet red and hematoxylin failed to show fat emboli. Baronofsky and his co-workers [13] have described the production of experimental gastric and duodenal ulcers in rabbits by combining intravenous oil injections with histamine subcutaneously.

---

11. Reuter, W., cited by Vance.[1b]

11a. Lindsay, S., and Moon, H. D.: Bone Marrow, Embolism Following Fracture, J. Bone & Joint Surg. **28**:377, 1946.

12. Scheriken, J. R., and Coleman, F. C.: Bone Marrow and Fat Embolism Following Fracture of the Femur, Am. J. Surg. **61**:126, 1943.

13. Baronofsky, I.; Merindino, K. A.; Bastrud, T. E., and Wangensteen, O. H.: Fate of Intravenously Injected Fat: Its Role in the Production of Ulcer, Proc. Soc. Exper. Biol. & Med. **59**:231, 1945.

Microscopically one observes that all parts of the lung are equally involved. Fat droplets are seen in capillaries of the alveolar walls and later in mononuclear phagocytes or in the edema fluid of the alveolar spaces. In addition to edema, there is often petechial hemorrhage and occasionally bronchopneumonia. In the kidneys little change is seen, aside from the presence of fat in the glomerular tuft capillaries; however, fat may also be present in the tubule epithelium and in the lumen. All parts of the central nervous system are uniformly involved [14] and, in addition to fat emboli, usually show perivascular edema, petechial hemorrhages, lymphocytic infiltration and multiple small areas of focal necrosis.

It has been found that the minimum lethal dose of neutral fat is higher than that of hydrolyzed fat in rabbits [15] and in dogs.[1a] Moreover, it has been said that the total amount of fat in the bone marrow of the femur is not great enough to cause death in human beings.[1b] For these reasons it has been suggested that fatty acids are actually responsible for tissue irritation. However, in our cases the reaction to Nile blue sulfate showed the fat to be neutral fat and not hydrolyzed. Warren [10] reported similar observations.

Death is usually the result of pulmonary edema and anoxia, but cardiac dilatation secondary to increased resistance in the pulmonary capillaries is common. DeTakats [5] suggested that thrombotic pulmonary emboli may cause death by vagal inhibition of the heart and by causing coronary vessel and bronchial tree constriction. About one fourth of the patients suffer cerebral deaths and show excessive involvement of the brain.[16]

Clinically the diagnosis of fat embolism is difficult to substantiate. Two clinical forms are notable, namely, one in which cardiorespiratory symptoms predominate and the other in which cerebral symptoms are outstanding. The onset may be sudden, but usually symptoms become manifest after the third or fourth day and in the cardiorespiratory type may consist of dyspnea, cough, frothy sputum with occasional hemoptysis, cyanosis, precardial pain, cardiac dilatation, elevation of temperature and often asthmatic or bronchopneumonic type rales. In the cerebral form symptoms are variable and include loss of memory, disorientation, restlessness, irritability and occasionally convulsions, which later give way to drowsiness, stupor and, finally, coma. In view of

14. (*a*) Gauss, H.: Studies in Cerebral Fat Embolism, Arch. Int. Med. **18**: 76, 1916. (*b*) Vance.[1b]

15. Harris, R. I.; Perrett, T. S., and MacLachlin, A.: Fat Embolism, Am. J. Surg. **110**:1095, 1939.

16. Gauss,[14a] Vance.[1b] Warren.[10]

the fact that delirium is so often followed by coma, a misdiagnosis of alcoholism in an injured patient is difficult to avoid.[17]

The diagnosis of fat embolism during life requires usually a history of trauma coupled with the typical clinical observations. Confirmatory diagnostic tests have been disappointing. Changes in blood fat concentration, blood specific gravity and blood surface tension are too variable to be of value; however, two tests, which are simple in execution, are fairly reliable.[17c] These are the demonstration of fat in the urine and of fat droplets in the blood by dark field examination. Fat is readily demonstrated in urine by Scuderi's "sizzle" test, in which an inoculation loop containing the urine sample is flamed. If fat is present a loud sizzling popping noise is heard. This test has been shown to be accurate in dilutions of 1:1400.[17c] It is important to remember that fat floats on the surface of the bladder urine and that only the last few cubic centimeters of urine will give a positive reaction. Moreover, if catheterization is necessary to obtain this urine, no lubricant may be used. The value of this test is decreased in the presence of diabetes, nephrosis, pyelonephritis, thoracic duct obstruction, phosphorous and alcohol poisoning or after the ingestion of a fatty meal.

Diagnosis is essential for rational therapy. It is obvious, then, that the treatment of any condition so often not even considered is apt to be far from satisfactory. The best treatment is prevention and consists of avoidance of rough handling of patients, immediate splinting, early reduction and fixation of fractures, the use of a tourniquet during operations on fatty marrow and the avoidance of fat solvent anesthetics.[18] Active therapy is poor. Suggested methods are the injection of sodium carbonate or bile salts, venesection, drainage of the thoracic duct, venous ligation, incision of the injured site to relieve pressure and to remove blood and fat and even amputation. Pituitrin, caffeine, coramine, morphine and insulin have been suggested because they have been found to cause a steady fall in the level of blood fat.[17c] Certainly the administration of oxygen is beneficial. None of these suggestions have received adequate trial, primarily because the diagnosis is usually forgotten.

CONCLUSIONS

1. Fat embolism is far commoner than is generally realized. As illustrated in this small autopsy series, 7 cases were discovered in

17. (*a*) deTakats, G.: Embolism, in Christopher, F.: Textbook of Surgery, ed. 3, Philadelphia, W. B. Saunders Company, 1942, p. 227. (*b*) Gauss.[14a] (*c*) Scuderi, C. S.: Fat Embolism: A Clinical and Experimental Study, Surg., Gynec. & Obst. **72**:732, 1941. (*d*) Wright.[1c]

18. deTakats.[17a] Scuderi.[17c] Vance.[1b]

which the disease was not diagnosed clinically or pathologically until frozen section and fat stains were done on lung and kidney samples. In most instances a diagnosis of pulmonary edema or bronchopneumonia had been made.

2. Clinicians must become fat embolism conscious, particularly in injured patients, and means must be found for confirmation of their bedside suspicions.

3. The dark field examination of the blood and the urine "sizzle" test seem to offer the most promise. Both of these diagnostic methods need further evaluation.

4. Until diagnosis becomes reliable no rational plan of active therapy can be formulated.

DISCUSSION

DR. J. DEWEY BISGARD, Omaha: In reviewing, a few years ago, a series of cases in which the postmortem explanation of death was fat embolism, I noticed that there were relatively few cases in which ether anesthesia had been given, so that I wondered whether ether might influence fat embolism and, possibly on the basis that it was a fat solvent, might somehow influence the fat. I might say that in a series of animals which my co-workers and I studied there was less fat in animals that had had ether anesthesia, but our study indicated that it was not on the basis of a solvent effect or breakdown as the result of ether anesthesia but a wider dilatation of the pulmonary capillary bed which permitted the fat to pass through more readily. I call your attention to Dr. Harris' observation that associated with fat embolism there is a sudden rapid drop in red cell count and this is suggestive if not partially diagnostic of the condition. Among the factors in prevention of fat embolism is slow release of the tourniquet, so that venous bleeding may wash out fat that has entered the vessels during operation. I wonder whether the refrigeration anesthesia used in amputations might not also prevent embolization of fat. As is known, fat is frozen to a rather stiff consistency and, being less liquid, is less likely to embolize. This might account for the fact that patients undergoing amputation with refrigeration anesthesia show less reaction to operation and less disturbance than occurs in patients with similar conditions operated on with other anesthetic agents.

ANATOMIC STUDY OF THE VAGUS NERVES

With a Technic of Transabdominal Selective Gastric Vagus Resection

RICHARD G. JACKSON, M.D.
ANN ARBOR, MICH.

IN THE treatment of duodenal ulcer by resection of the vagus nerve supply to the stomach, knowledge of the anatomy of the vagus nerves is of fundamental importance. The purpose of this paper is to present the results of a study of these nerves carried out in the Department of Anatomy of the University of Michigan between October 1946 and April 1947 and to suggest a new technic of transabdominal vagus resection based on this study. The vagus nerves have been described by Swan,[1] Bourgery,[2] Kollman,[3] Perman,[4] Latarjet,[5] McCrea,[6] Mitchell[7] and recently by Miller and Davis,[8] Bradley, Small, Wilson and Walters,[9] Chamberlin and Winship[10] and by Dragstedt, Fournier, Woodward, Tovee and Harper.[11] In a preliminary report of this anatomic study[12] the literature on the subject was summarized and as a complete report containing this summary will be published elsewhere, it will not be repeated here. Certain facts of surgical significance, however, will be given.

This study was aided by the John Harper Seeley Foundation.

From the Departments of Surgery and Anatomy, University of Michigan, Ann Arbor.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

1. Swan, J.; A Demonstration of the Nerves of the Human Body, London, Longman [and others], 1834, plates 3, 4 and 7.

2. Bourgery, M. J.: Traité complet de l'anatomie de l'homme, Paris, C. A. Delaunay, 1844, vol. 3, plates 42 and 43.

3. Kollman: Ztschr. f. wissensch. Zool. **10**:413, 1860.

4. Perman, E.: Ark. f. Zool. **10**:1, 1916.

5. Latarjet, A.: Bull Acad. de méd., Paris **87**:681, 1922.

6. McCrea, E. D.: J. Anat. **59**:18, 1924; Brit. J. Surg. **13**:621, 1925.

7. Mitchell, G. A. G.: Brit. J. Surg. **26**:333, 1938.

8. Miller E. M., and Davis, C. B.: Anatomic Study of Vagus Nerves, J. A. M. A. **133**:461 (Feb. 15) 1947.

9. Bradley, W. F.; Small, J. T.; Wilson, J. W., and Walters, W.: Anatomic Considerations of Gastric Neurectomy, J. A. M. A. **133**:459 (Feb. 15) 1947.

10. Chamberlin, J. A., and Winship, T.: Surgery **22**:1, 1947.

11. Dragstedt, L. R.; Fournier, H. J.; Woodward, E. R.; Tovee, E. B., and Harper, P. V.: Surg., Gynec. & Obst. **85**:461, 1947.

12. Jackson, R. G.: Univ. of Michigan Hosp. Bull. **13**:31, 1947.

In this study the vagus nerves were first dissected above the diaphragm in 50 cadavers, starting just below the pulmonary plexus and following them to the diaphragm. The specimens used were those being dissected by medical and postgraduate anatomy students. In every case the dissection was done before the student reached the area in his dissection, the nerves were charted and, after the heart had been

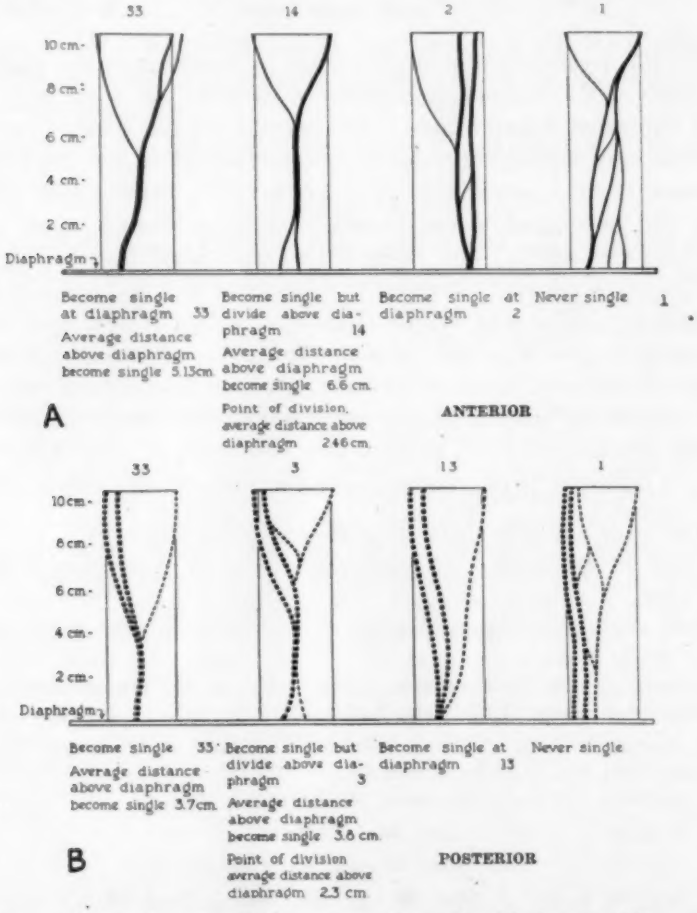


Fig. 1.—*A*, formation of anterior vagus above the diaphragm (50 persons). The left vagus forms the major portion, but usually receives communicating branch or branches from the right vagus. Four types of trunks are shown. *B*, formation of the posterior vagus above the diaphragm (50 persons). It differs from the anterior vagus in that the major portion comes from the right vagus, the formation of single trunks generally occurs lower on the esophagus than with the anterior and more often does not occur until the diaphragm is reached.

removed and the student was ready for the dissection of the esophageal plexus, they were checked again to be sure that no branches had been missed. After the student had studied the nerves, a number of them were photographed to show the disposition of the main trunks and

branches. In some cadavers branches found and recorded in the original diagram were broken by the students in their examinations and therefore do not appear in the photographs, but they do appear in the drawing beside the photograph. The chief value of the photographs is in showing the size of the trunks and their approximate location on the esophagus. Only the main trunks and divisions, the communicating branches and the larger esophageal branches were charted; the pericardial, the diaphragmatic and the aortic branches were not charted. This reduces considerably the apparent complexity of the arrangement of the nerves on the esophagus and makes clearer the course of the trunks destined for viscera below the diaphragm. In the majority of dissections, however, esophageal, pericardial, diaphragmatic and aortic branches were seen, and in one dissection a communicating branch between a sympathetic chain ganglion and the posterior vagus was found.

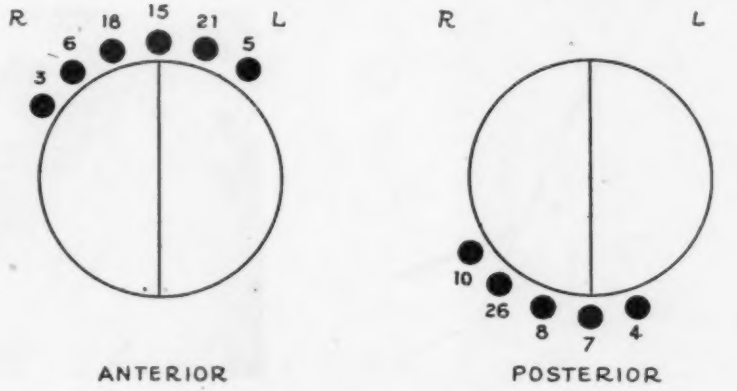


Fig. 2.—Position of anterior and posterior vagus on cross section of the esophagus at the diaphragm, seen from below the diaphragm.

The following measurements were made:

(*a*) The distance above the diaphragm that the branches from the right and left vagus joined to form single trunks was recorded.

(*b*) In some instances the single trunks divided again before passing through the diaphgram. In these instances the distance above the diaphragm at which this division occurred was measured.

Four types of anterior and posterior vagus nerve trunks were seen (fig. 1). Type A became single above the diaphragm and passed through the diaphragm as a single trunk. Type B became single above the diaphragm but divided into two or three trunks before passing through the diaphragm. Type C became single at the diaphragm. Type D was never single above the diaphragm. Analysis of the anterior vagus shows that there were 33 type A, 14 type B and 2 type C trunks and one type D trunk. Thus 47 of the 50 anterior trunks became sin-

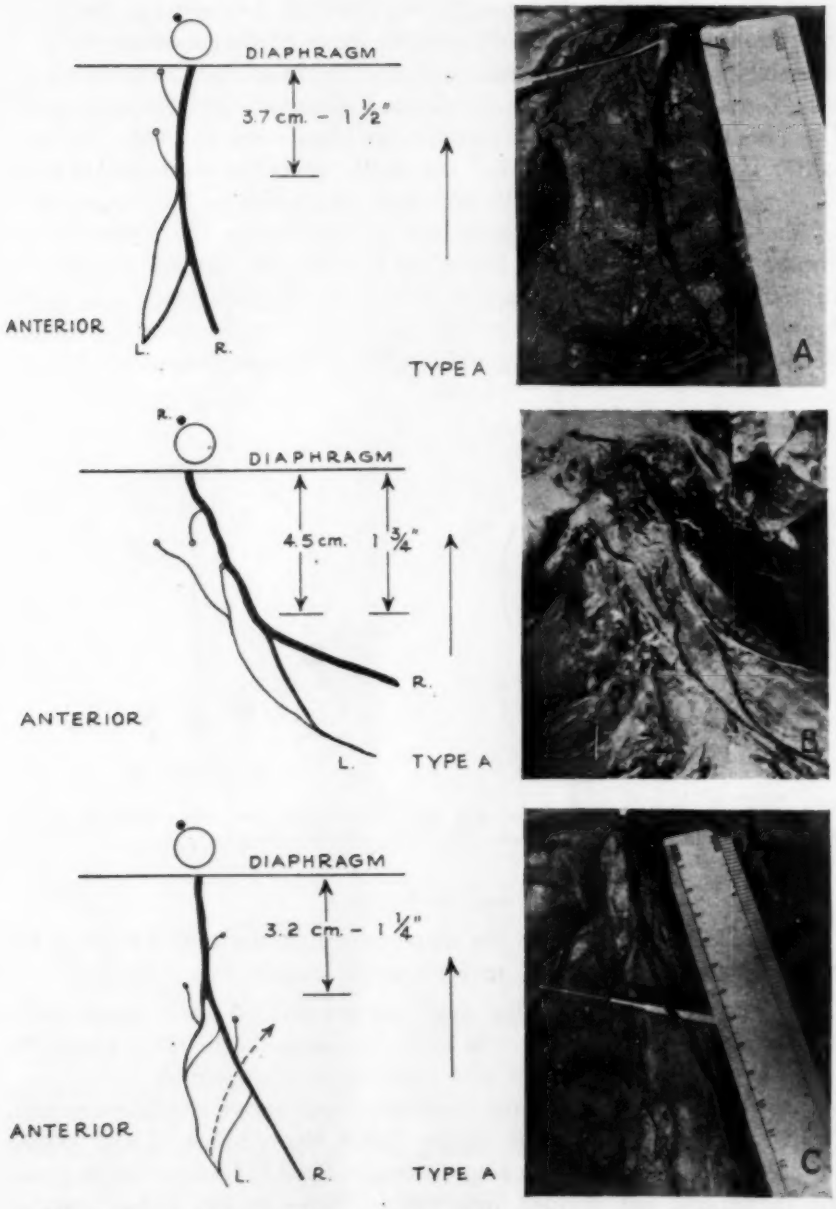


Fig. 3.—Example of anterior type A trunks. Cross sections show location of the trunk on the esophagus as seen from below the diaphragm.

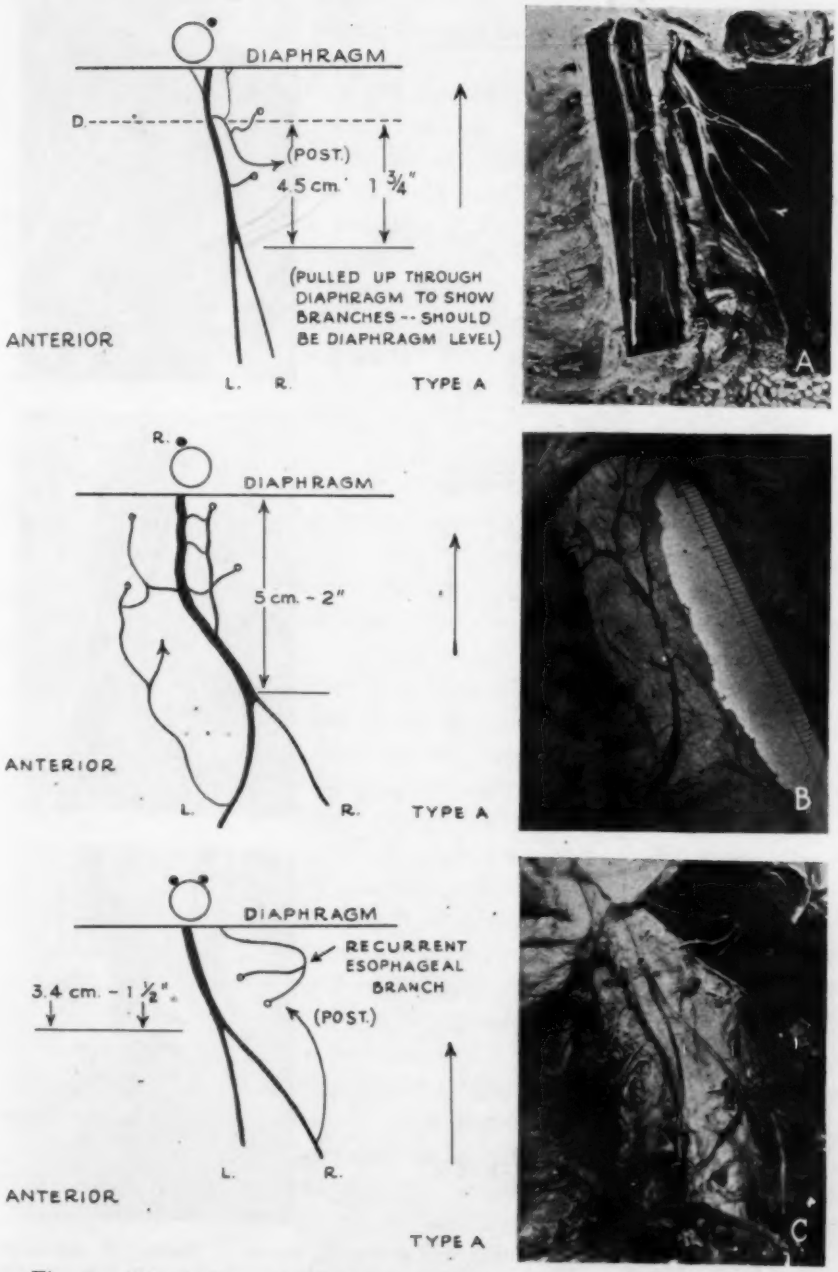


Fig. 4.—Anterior type A trunks. *A*, a low communicating branch between anterior and posterior trunks is shown. The posterior trunk has been pulled to the right from behind the esophagus. *C*, an esophageal branch which arose from the anterior trunk below the diaphragm and came back through the diaphragm is shown.

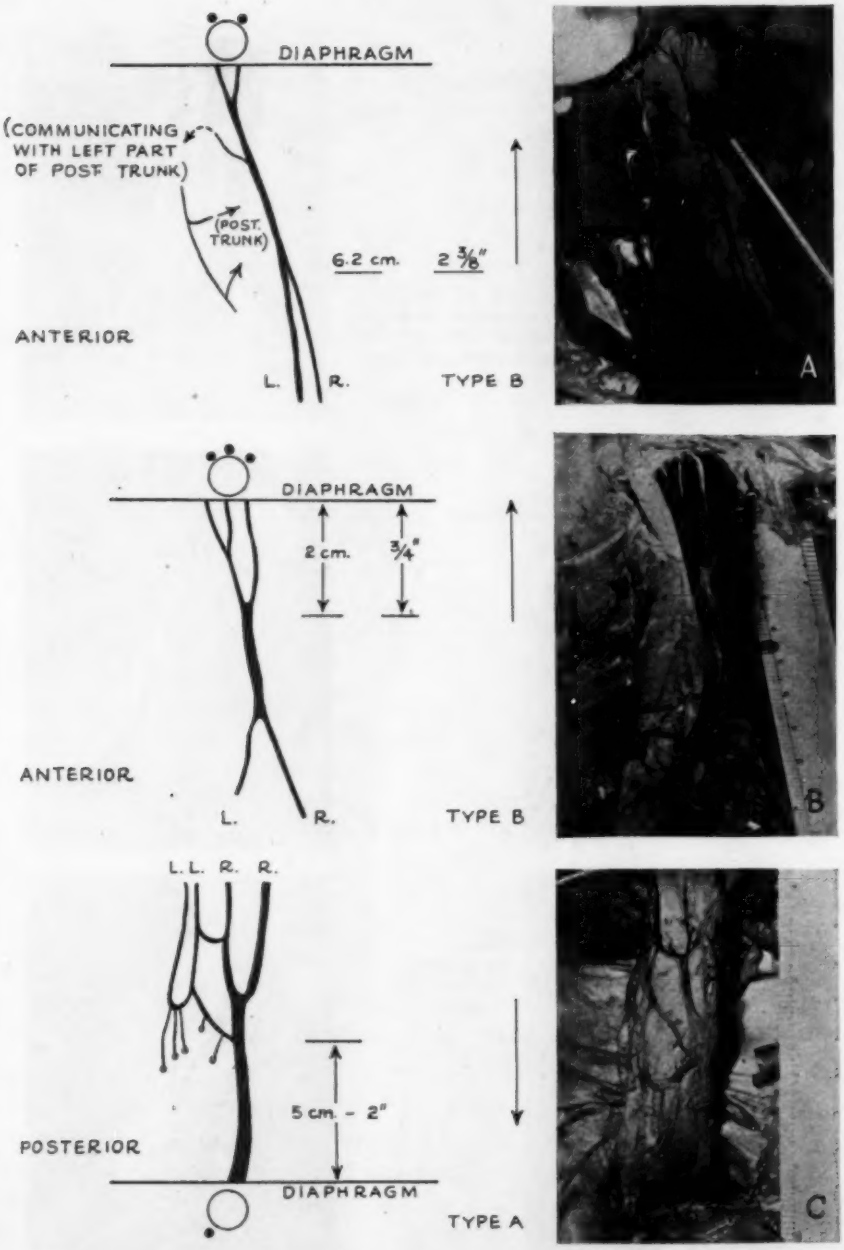


Fig. 5.—Type B anterior trunks and a type A posterior trunk. *A*, the communicating branch between the anterior and posterior trunks ran through the muscle of the esophageal wall. *C*, the esophagus has been cut at the level of the hilum of the lung and lifted forward to expose its posterior surface. Formation of the posterior vagus which goes through the diaphragm as a single trunk is shown.

gle at some point between the pulmonary plexus and the diaphragm. Analysis of the posterior vagus shows a different occurrence of types: 33 were type A; 3 were type B; 13 were type C, and 1 was type D. Thus 36 became single above the diaphragm, while 13 did not become single until the diaphragm was reached.

The average distance above the diaphragm that the anterior trunk became single was 5.13 cm. and the posterior trunk 3.7 cm. In the fourteen anterior and three posterior trunks which divided again before passing through the diaphragm the point at which they became single averaged 6.67 cm. above the diaphragm for the anterior and 3.8 cm. for the posterior; the point of division averaged 2.46 cm. for the anterior and 2.3 cm. for the posterior. Thus the anterior trunks generally became single farther above the diaphragm than did the posterior trunks, and more of the anterior trunks divided again before passing through the diaphragm (28 per cent of the anterior, 6 per cent of the posterior). The type B anterior trunks were single for a longer distance before dividing than the type B posterior trunks. The posterior trunks more often did not become single until they reached the diaphragm—there were more type C trunks posteriorly than anteriorly.

The communicating branches were analyzed as follows: Branches passing between the right and left vagus in the inch above the diaphragm were called "low" communicating branches; those which communicated in the second inch above the diaphragm were called "middle," and those above 2 inches (5 cm.) were called "high" communicating branches; those which arose high but did not communicate until the last inch were called "long" communicating branches. Generally, branches from the right to the left vagus passed anterior, those from the left to the right passed posterior. Examples of anterior "high" communicating branches are shown in figures 4*B*, 5*A* and 5*B*, of the anterior "middle" communicating branches in figures 3, 4*A* and 4*C*, of posterior "high" communicating branches in figures 5*C* and 6*A*, of posterior "middle" and "long" types in figures 6*B* and of posterior "long" types in figures 6*C*, 7*B* and 7*C*. Occasionally a communicating branch which passed through the muscle of the esophagus between the anterior and posterior trunks was seen (fig. 5*A*). Communicating branches were not found in all dissections; occasionally more than one anterior and/or more than one posterior communicating branch were found, and the combinations are recorded in table 1.

It is interesting that, as shown in table 1 a single posterior trunk was not often formed above a point 2 inches (5 cm.) above the diaphragm (7 cases) while a single anterior trunk was formed above this point more often (19 cases). Another interesting point and one that

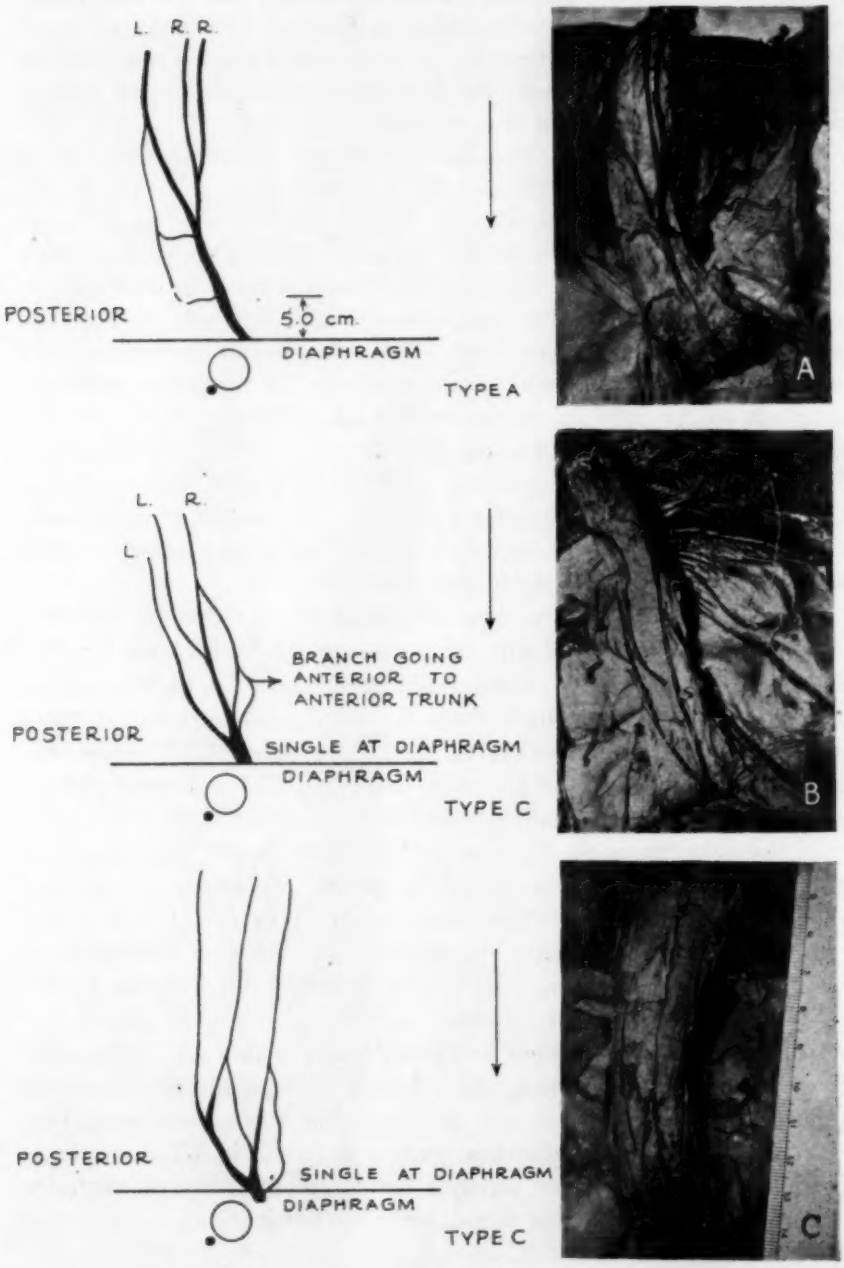


Fig. 6.—Posterior trunks, types A and C. *B* and *C*, a single posterior trunk is not formed until the diaphragm is reached. Long communicating branches from the left vagus to the right vagus are shown.

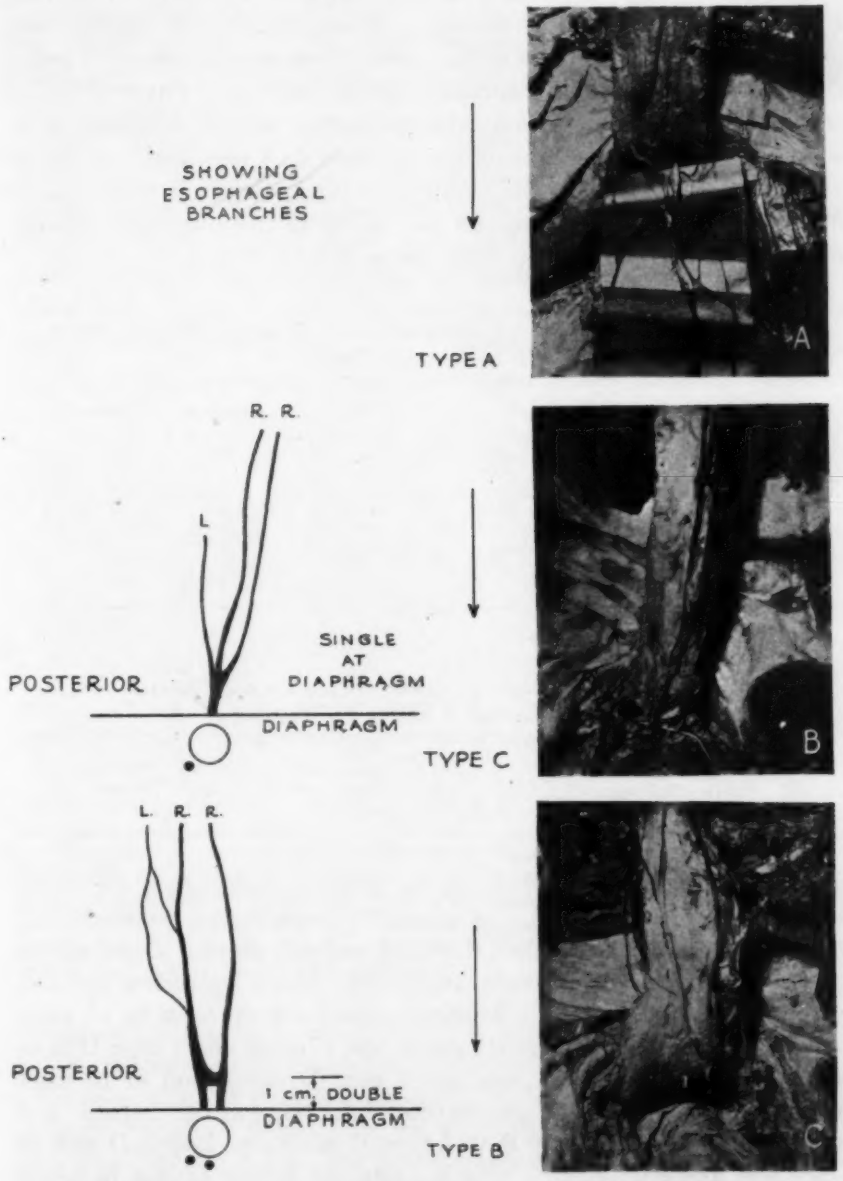


Fig. 7.—Posterior vagus trunks, types A, B. and C. *A*, esophageal branches are shown. *C*, posterior vagus goes through the diaphragm as a double trunk.

with the foregoing statement may explain some of the failures in supradiaphragmatic vagus resections is the relatively large number of long communicating branches posteriorly. If one sections the anterior and posterior vagus trunks there is the chance of being either above or below the short communicating branches (whether high or low types) and of cutting all the fibers; the long communicating branch, however, or in some cases the middle communicating branch, if one does not find it separately, will maintain the continuity. Occasionally a communicating branch which passed through the muscle of the esophagus between the anterior and posterior trunks was seen (fig. 5 *A*).

TABLE 1.—*Supradiaphragmatic Communicating Branches Between Right and Left Vagus Nerves*

	Anterior	Posterior
High	19	7
Middle	13	20
Low	1	1
Long	2	15
High and middle	4	1
High and long	1	1
Middle and long	1	1
Middle, long and low	..	1
None	9	3

TABLE 2.—*Occurrence of Multiple Trunks in the Area 2 Inches (5 Cm.) Above and 2 Inches Below the Diaphragm*

	Cases	Anterior	Posterior
Above diaphragm	17	3	14
Below diaphragm	19	15	4

The question arises, "May one be surer of dividing all the vagus trunks above or below the diaphragm?" Since failure to section all the trunks is more likely when there are multiple trunks, a comparison of the occurrence of multiple trunks just above and below the diaphragm should be of value. Multiple trunks were present in 17 cases above the diaphragm (anteriorly the 2 type C cases and 1 type D case, posteriorly the 13 type C cases and 1 type D case), and in 19 cases below the diaphragm—before division into the gastric, hepatic and other branches—(anteriorly the 14 type B cases and 1 type D case in figure 1 *B*, posteriorly the 3 type B cases and 1 type D case in figure 1 *A*). Above the diaphragm 14 of 17 were posterior and 3 anterior, and below the diaphragm 4 of 19 were posterior and 15 anterior (table 2). Since it should be easier to find multiple trunks on the anterior than on the posterior surface, it would seem that vagus section should be surer on the subdiaphragmatic esophagus where the multiple trunks are

more often anterior than just above the diaphragm where they are more often posterior. Another solution would be to divide the anterior vagus just above the diaphragm since it usually becomes single higher than the posterior trunk, and to divide the posterior vagus just below the diaphragm, since it more often does not become single until the diaphragm is reached.

In the fifty dissections below the diaphragm, the anterior trunk was traced downward, the gastric branches followed until they disappeared into the stomach wall and their area of distribution charted. The point of origin of the hepatic branch was noted. The posterior vagus was similarly traced, the gastric branches charted and the point of origin of the celiac division noted. In the first cadaver dissected, the hepatic branch of the anterior trunk was followed to its termination and its

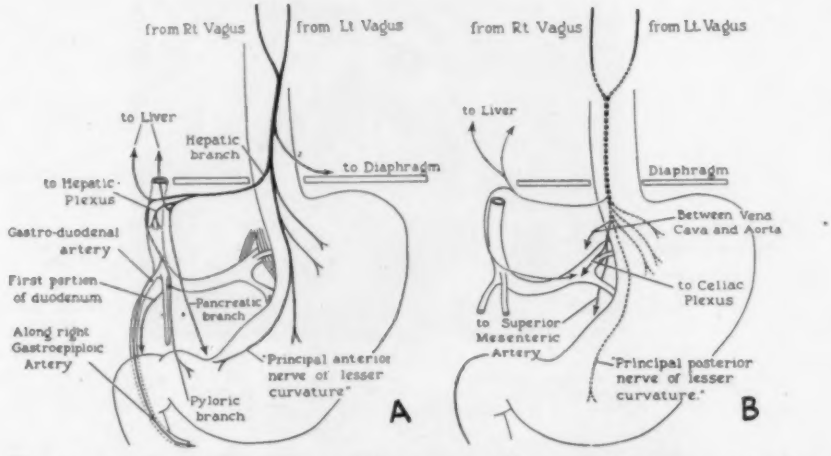


Fig. 8.—*A*, dissection of the anterior vagus below the diaphragm, showing the hepatic branch and its distribution. The branch to the pyloric region of the stomach came from the hepatic branch and reached the stomach along the right gastric artery. *B*, dissection of the posterior vagus below the diaphragm. A hepatic branch was found in this dissection. No gastric supply arose from this branch. This dissection is shown in figure 9.

branches are shown in figure 8 *A*. It will be noted that the supply to the pyloric region comes from this branch. In this cadaver, an attempt was made to follow the celiac division of the posterior vagus through the celiac plexus. In the remainder of the dissections, attention was concentrated on the gastric branches, the hepatic branch was followed only to the fissure for the ductus venosus and the celiac division only to the celiac plexus. The celiac division could not be followed through the celiac plexus. It became lost in the plexus, and one could not say whether the fibers emerging from the plexus were sympathetic or parasympathetic. In figure 8 *B* this dissection of the poste-

rior vagus is shown. An hepatic branch arose from the posterior trunk in this specimen and it communicated with the celiac plexus; no gastric supply arose from this branch.

The average number of gastric branches from the anterior trunk was four, although one to nine branches were seen. They were distributed to the proximal part of the stomach along the lesser curvature, with a branch occasionally almost reaching the greater curvature. In 2 cases no gastric branches were seen; only an hepatic branch was noted. The "principal anterior nerve of the lesser curvature" described by Latarjet was found in 28 instances. This branch sometimes passed

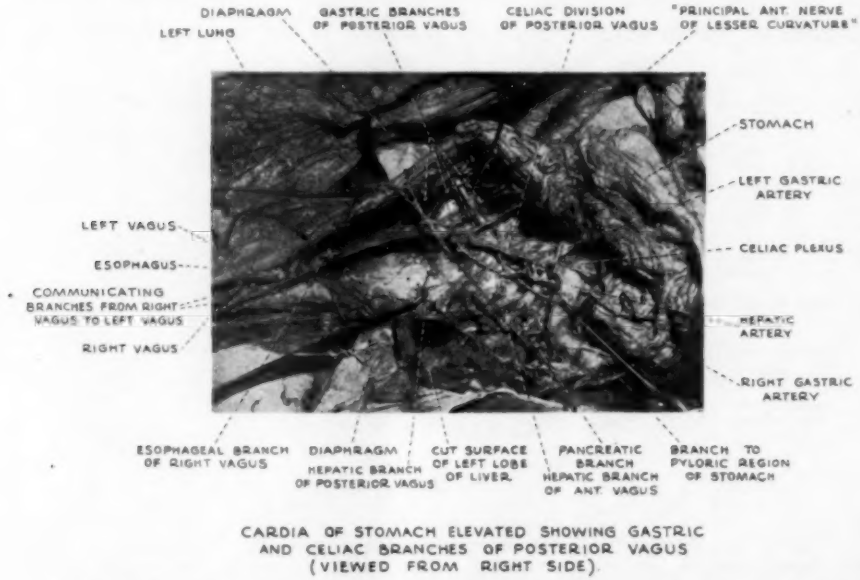

DIAPHRAGM
LEFT LUNG
GASTRIC BRANCHES OF POSTERIOR VAGUS
CELIAC DIVISION OF POSTERIOR VAGUS
"PRINCIPAL ANT. NERVE OF LESSER CURVATURE"
STOMACH
LEFT GASTRIC ARTERY
CELIAC PLEXUS
HEPATIC ARTERY
RIGHT GASTRIC ARTERY
LEFT VAGUS
ESOPHAGUS
COMMUNICATING BRANCHES FROM RIGHT VAGUS TO LEFT VAGUS
RIGHT VAGUS
ESOPHAGEAL BRANCH OF RIGHT VAGUS
DIAPHRAGM
HEPATIC BRANCH OF POSTERIOR VAGUS
CUT SURFACE OF LEFT LOBE OF LIVER
PANCREATIC BRANCH
HEPATIC BRANCH OF ANT. VAGUS
BRANCH TO PYLORIC REGION OF STOMACH
CARDIA OF STOMACH ELEVATED SHOWING GASTRIC AND CELIAC BRANCHES OF POSTERIOR VAGUS (VIEWED FROM RIGHT SIDE)

Fig. 9.—Dissection of the posterior vagus viewed from the right side of the cadaver. The gastric branches of the posterior vagus and the celiac division are shown.

along the lesser curvature and sometimes passed from the anterior trunk high on the stomach through the lesser omentum near the lesser curvature, usually behind the left gastric artery, returning to the stomach generally from 1 to 3½ inches (2.5 to 9 cm.) from the pylorus. The hepatic branch was seen in all but 7 cases. Two hepatic branches were seen in 2 cases and five in 1 case. The hepatic branch left the anterior trunk just below the diaphragm (occasionally just above the diaphragm), and passed through the lesser omentum to run in the fissure for the ductus venosus to the porta hepatis. An anterior plexus was found in 1 case.

The anatomy of the posterior vagus was particularly interesting. In all cadavers the costal arch and diaphragm were intact and the liver in place. In figure 9 a dissection in which the diaphragm has been cut and part of the liver removed for better illustration is shown. It became evident that the nerve could be most readily found in the cadaver by incising the lesser omentum at the point where the left gastric artery reached the stomach (fig. 10) or, if it was not there, in the triangular area bounded on the right by the right crus of the diaphragm, on the left by the edge of the stomach and below by the left gastric artery. The variations in the course of the posterior trunk and in the origin of the celiac division were as follows (fig. 11):

1. In 20 cases the posterior trunk descended along the lesser curvature of the stomach and the celiac division was given off when the

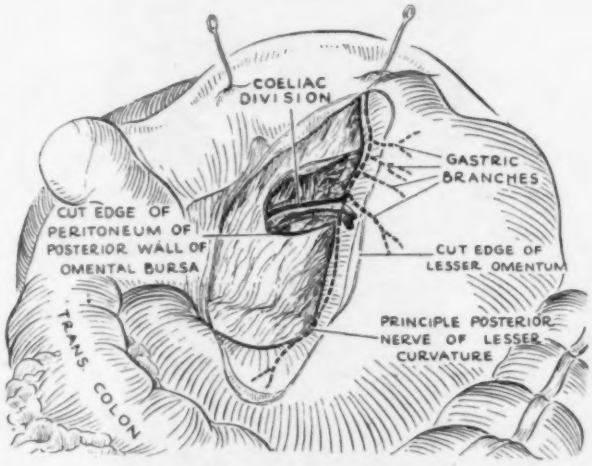

COELIAC DIVISION
GASTRIC BRANCHES
CUT EDGE OF PERITONEUM OF POSTERIOR WALL OF OMENTAL BURSA
CUT EDGE OF LESSER OMENTUM
PRINCIPLE POSTERIOR NERVE OF LESSER CURVATURE
TRANS. COLON

Fig. 10.—The posterior vagus, showing the course of the celiac division which was found in 20 cases.

trunk reached the left gastric artery and ran along the superior surface of the artery to the celiac plexus (fig. 10).

2. In 14 cases the celiac division arose somewhere between the point at which the left gastric artery reached the stomach and 1 inch (2.5 cm.) above this point and ran to the right to reach the left gastric artery (fig. 12*A*).

3. In 9 cases the posterior trunk left the esophagus just below the diaphragm and ran to the right along the crus of the diaphragm and then along the aorta to the celiac plexus, giving off gastric branches along its course (fig. 13).

4. In 5 cases the posterior trunk ran as described in 3, but gave off a gastric branch late, just before reaching the celiac plexus. This

branch ran back along the left gastric artery or the coronary vein to the stomach (fig. 12 *B*).

5. In 1 case the celiac division left the posterior trunk just below the diaphragm and ran down along the aorta to the celiac plexus, while the gastric portion of the trunk ran down on the stomach.

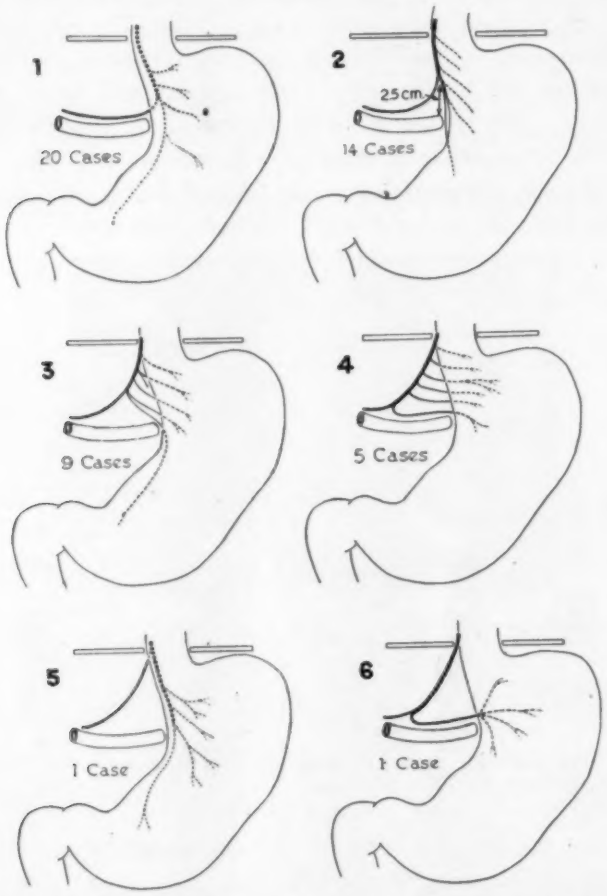


Fig. 11.—Variations in the course of the posterior vagus and its celiac division.

6. In 1 case the posterior trunk left the esophagus just below the diaphragm and ran down along the crus and then along the aorta to the celiac plexus. Just before it reached the plexus, a gastric division emerged to run along the left gastric artery to the stomach where five branches passed into the stomach wall.

The average number of branches from the posterior trunk was six, although one to fifteen were seen, and gastric branches were found in

all cases. The "principal posterior nerve of the lesser curvature" of Latarjet was found in 19 cases. It ran along the lesser curvature toward the pylorus and then turned across the posterior surface of the stomach, usually accompanying a vessel toward the greater curvature, occasionally almost reaching it. No branch, anterior or posterior,

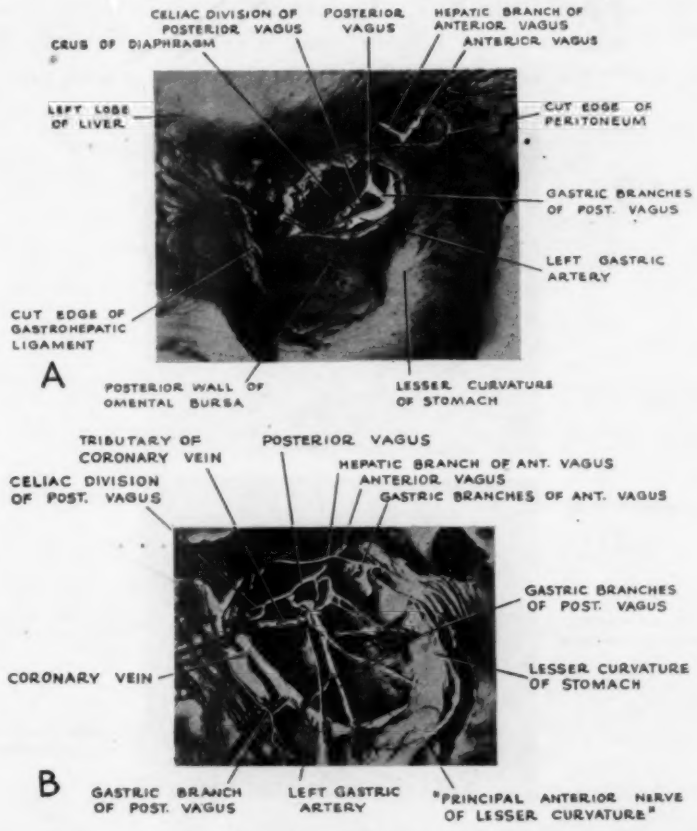


Fig. 12.—*A*, retouched photograph showing another frequently observed origin of the celiac division of the posterior vagus (fig. 11 [2], 14 cases). The peritoneum on the esophagus has been cut to reveal the anterior vagus and its hepatic division. *B*, retouched photograph of dissection of posterior vagus, showing the course of the posterior trunk as in figure 11 (4). The gastric branches are shown. One gastric branch arose just before the celiac division reached the left gastric artery near the celiac plexus to run back along the coronary vein to the stomach. The anterior vagus is shown also.

reached the duodenum by passing along the stomach. The closest any branch came to the pyloric sphincter was 2.5 cm. A posterior plexus was found in one dissection.

OPERATIVE TECHNIC; TRANSABDOMINAL SELECTIVE GASTRIC VAGUS RESECTION

These dissections suggest that it is possible to remove the vagus supply to the stomach, and preserve in the posterior trunk and its celiac division the vagus supply to the spleen, kidneys, adrenals, part of the pancreas, the small intestine below the first portion of the duodenum, the colon and part of the liver. The technic shown in figure 14 is suggested. A segment of the anterior trunk is removed above the hepatic branch—above the hepatic branch because from this branch comes the

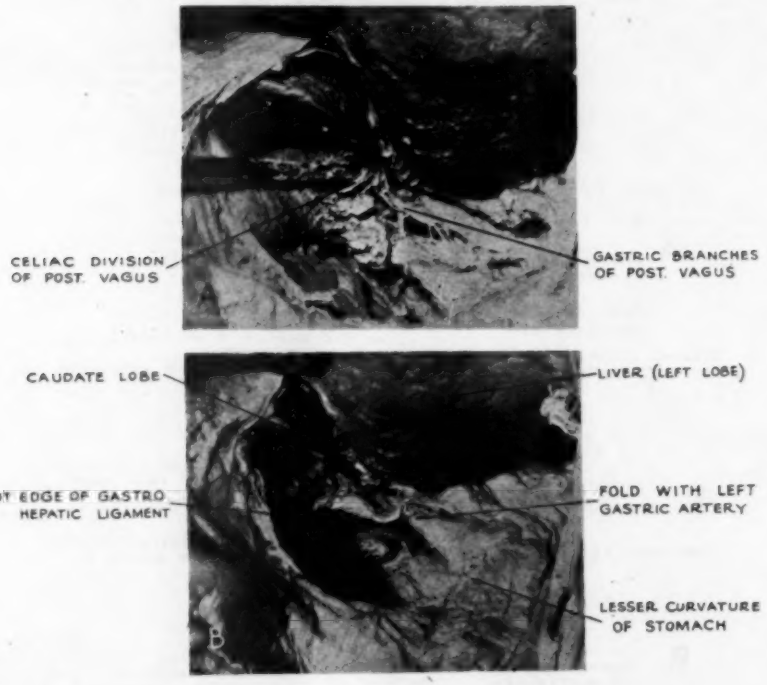


Fig. 13.—Photographs before (*B*) and after (*A*) dissection of the posterior vagus in a patient with a large tuber omentale of left lobe of liver and an extension of the omental bursa upward behind the left gastric artery. Origin of the celiac division as shown in figure 11 (3).

branch to the pyloric portion of the stomach. It would be theoretically possible to find the pyloric branch on the right gastric artery and save the branches to the liver, pancreas, first portion of the duodenum and biliary tract, but this branch is small and could easily be missed. The proximal end of the cut anterior trunk is turned up and sutured to the diaphragm or outside the peritoneum on the stomach. Since in the dissections above the diaphragm, fifteen of fifty (30 per cent) of the anterior trunks came through the diaphragm as two or three divisions,

the surgeon must carefully look for other divisions after sectioning the one first found. The hepatic branch of the anterior vagus is also sectioned, since in one dissection a communicating branch from the posterior vagus to the hepatic branch was seen. The posterior vagus is then exposed in the region described above by cutting the gastrohepatic omentum and the peritoneum on the posterior wall of the omental bursa. It is followed upward from the celiac division, removing a 1 to 1.5 cm. segment of each of the gastric branches, but leaving the main

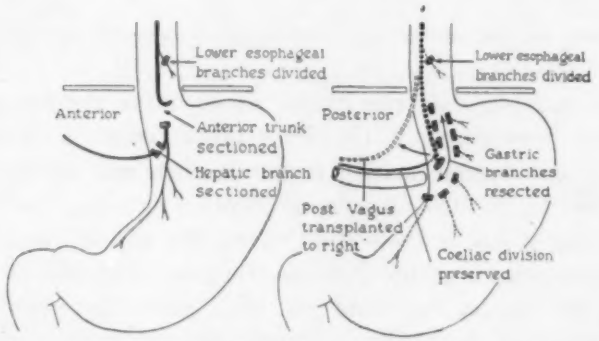


Fig. 14.—Operative technique of selective gastric vagus resection.

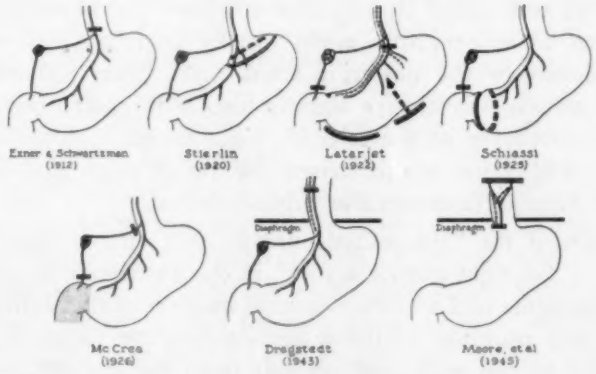


Fig. 15.—Methods of vagus resection.

trunk and celiac division intact. If the trunk lies on the stomach it may be transplanted to the right onto the diaphragm over the aorta to prevent regenerating fibers from reaching the stomach. Eight per cent of the posterior trunks come through the diaphragm as two divisions, and the gastric divisions should be searched for and cut. Since the impulses from the vagus apparently spread through a nerve net in the stomach wall (Stohr [13]), as well as by the myenteric plexuses

13. Stohr, P., Jr.: Ztschr. f. Zellforsch. u. mikr. Anat. **21**:243, 1934.

(Hill [14]), it seems likely that impulses from lower esophageal branches might spread onto the proximal portion of the stomach. It is recommended, therefore, that where possible the trunks or the esophagus be pulled down through the diaphragm and the lower esophageal branches from the anterior and posterior trunks sectioned. If it were not necessary to cut these branches they might be left and the possibility of achalasia of the esophagus prevented.

COMMENT

A review of the literature reveals the following technics of vagus section:

1. Section of the anterior trunk alone, above the liver branch—(Exner and Schwarzman,[15] 1912) for tabetic crises.

2. A circumferential incision of the stomach wall to mucosa at the cardia—(Stierlin,[16] 1920) for peptic ulcer.

3. Section of the anterior trunk below the hepatic branch; section of the pyloric branch on the right gastric artery; section of the omentum along the greater curvature just proximal to the pylorus, and by going through the gastrocolic omentum and using the coronary vein as a guide, cutting the principal posterior nerve of the lesser curvature and any other gastric branches of the posterior trunk that could be found. It was stated that by this approach the principal posterior nerve of the lesser curvature could usually be found, but the higher gastric branches of the posterior trunk were often difficult to find. The vagus section was always accompanied with gastroenterostomy to allow better emptying of the stomach made atonic by vagus section—(Latarjet,[17] 1922) for tabetic crises, for peptic ulcer and for gastric complaints without demonstrable organic lesion.

4. Section of the "sympathetic nerves, two on the right and four on the left of the right gastric artery" in the gastrohepatic and hepatoduodenal ligaments and a circumferential incision of the stomach almost to mucosa just proximal to the pylorus to cut the vagus fibers which were thought to run with small vessels from the stomach to the duodenum. The purpose of this operation was to put the pyloric region and the duodenum at rest. A gastroenterostomy was done also—(Schiassi,[18] 1925) for peptic ulcer.

5. Section of the pyloric branch of the hepatic branch of the anterior vagus on the right gastric artery and stripping of nerve fibers from

14. Hill, C. J.: Phil. Tr. Roy, Soc., London, s. B **215**:355, 1927.
15. Exner, A., and Schwarzman, E.: Wien. klin. Wchnschr. **25**:1405, 1912.
16. Stierlin, E.: Deutsche Ztschr. f. Chir. **152**:358, 1920.
17. Latarjet, A.: Bull. Acad. de med., Paris. **87**:681, 1922.
18. Schiassi, B.: Ann. Surg. **81**:939, 1925.

beneath the serosa of the pylorus and first part of the duodenum—(suggested by McCrea,[19] 1925) for peptic ulcer.

6. Total section of the anterior and posterior vagus trunks above the diaphragm—(Dragstedt,[20] 1943) for duodenal ulcer.

7. Removal of the entire vagus system from just below the pulmonary plexus to the diaphragm—(Moore, Chapman, Schulz and Jones,[21] 1946) for duodenal ulcer.

The procedures of Stierlin and Latarjet come closest to gastric vagal denervation without section of the celiac division. In Stierlin's circumferential incision operation, however, the branches to the proximal portion of the cardia are left, and in those cases in which the posterior trunk runs to the right below the diaphragm giving off gastric branches at different levels on its way to the celiac plexus, these gastric branches would be missed. Latarjet reported one of the best of the early anatomic studies and based his method on it. In his approach through the gastrocolic omentum, however, he stated that one was not certain of finding all the posterior gastric branches. It is felt that the approach through the gastrohepatic ligament advocated in this paper is more direct and accurate and should allow removal of all gastric branches which have been demonstrated in dissections.

The possibility that the celiac division of the posterior vagus might give off branches to the stomach after it had passed through the celiac plexus has been considered in this study. If it is assumed that branches of the celiac division pass from the celiac plexus along the splenic artery to the spleen, these branches might give off branches to pass along the left gastroepiploic and short gastric arteries to the greater curvature of the stomach, and vagal branches might pass from the celiac plexus along the hepatic artery and thence along the right gastric and gastroepiploic arteries to the stomach. The presence of such branches could not be proved, because the posterior vagus could not be traced through the celiac plexus. It became lost in the plexus, and one could not say whether fibers emerging from the plexus were sympathetic or parasympathetic. Microscopic study of sections of the nerves on the gastroepiploic and short gastric arteries with preparations to show myelin would differentiate between the preganglionic myelinated vagus fibers and the postganglionic nonmyelinated sympathetic visceral efferent fibers, but not between the myelinated vagus and the myelinated sympa-

19. McCrea, E. D.: Brit. J. Surg. **13**:621, 1925.

20. Dragstedt, L. R., and Owen, F. M.: Proc. Soc. Exper. Biol. & Med. **55**:152, 1943. Dragstedt, L. R., and Schafer, P. W.: Surgery **17**:742, 1945. Dragstedt, L. R.; Palmer, W. L.; Schafer, P. W., and Hodges, P. C.: Gastroenterology **3**:450, 1944.

21. Moore, F. C.; Chapman, W. P.; Schulz, M. D., and Jones, C. M.: New England J. Med. **234**:241, 1946.

thetic afferent fibers. That such branches are probably not present, or at least are not significant is suggested by the fact that complete vagal denervation of the stomach has been accomplished by selective vagus section in patients as shown by preoperative and postoperative insulin tolerance tests and motility studies.

Transabdominal selective gastric vagus resection has been performed in this clinic in 16 cases. In 13 of these cases a gastroenterostomy was also done because of obstruction at the duodenal ulcer site. It is too early to report the clinical results; a detailed report will be presented later, and the results following selective section will be compared with those following total section. It can be stated now, however, that the method has been found technically feasible by the resident staff at the University of Michigan and as checked by insulin tolerance tests and motility studies carried out before operation and at intervals after operation that all gastric vagal innervation can be removed by this procedure.

SUMMARY

The anatomy of the vagus nerves on the esophagus below the pulmonary plexus and in their gastric distribution has been described. A technic of transabdominal vagus resection is suggested in which the vagal innervation of the stomach is removed, but the innervation of the small intestine below the first portion of the duodenum, of the large intestine as far as the distal portion of the transverse colon, the kidneys, adrenals, spleen, and part of the liver and pancreas is preserved.

RESULTS OF RESECTION OF THE VAGUS NERVE FOR CHRONIC PEPTIC ULCER

EDWIN M. MILLER, M.D.
AND
JOHN H. OLWIN, M.D.
CHICAGO

IT IS fair to say that the management of patients with peptic ulcer is still largely a medical problem, inasmuch as most authorities agree that only about 15 per cent need surgical intervention. The work of Dragstedt and his associates has opened up a new approach to the surgical attack, and in many clinics studies are now in progress seeking to determine the permanent value of vagus nerve resection in those patients in whom medical treatment has not been successful.

SCOPE OF THIS PAPER

Our study attempts to evaluate results in a series of 101 patients subjected to vagotomy in the past two and a half years, 66 of whom were operated on at the Veterans' Hospital at Hines, Ill., and 35 at the Presbyterian Hospital in Chicago. It involves the work of eighteen different surgeons, all members of the American Board of Surgery, and several medical men in these institutions.

PATHOLOGIC ASPECT

For the most part these 101 patients had long-standing chronic peptic ulcer and, for one reason or another, had failed to do well on a medical regimen. In more than half the duration was over ten years, the longest being forty years. In 87 the lesion was in the duodenum, in 5 on the lesser curvature of the stomach and in 8 at the stoma after gastroenterostomy or gastric resection. In 47 there was a history of bleeding (often several times repeated); 26 had had perforations, and in 36 obstruction was demonstrable clinically or by roentgenogram. They represented, therefore, situations in which the surgeon was called on to decide between gastroenterostomy, a partial gastrectomy or a resection of the vagus nerves either above or below the diaphragm.

From the Veterans' Hospital, Hines, Ill., and the Presbyterian Hospital, Chicago.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

SURGICAL TREATMENT

In this series of 101 vagotomies the transthoracic approach was employed in 29, seventeen times for duodenal ulcer without obstruction, six times for gastrojejunal ulcer without obstruction and once for gastric ulcer without obstruction. In 4 cases, unfortunately, it was chosen as the route when obstruction was present, and in each instance it proved to be an unwise decision. In 72 patients vagotomy was accomplished by the abdominal approach; in 16 of these it was used alone, and in 56 combined with gastroenterostomy.

POSTOPERATIVE COURSE

The postoperative course was in most cases remarkably smooth. The Levine tube was always left in place three or four days. Early ambulation was encouraged. One patient with pneumothorax was at once relieved by aspiration. A few patients had a mild pleural effusion and pain in the chest for several days, but in only 1 instance was it a prominent feature in the months following operation. One woman had trouble swallowing for almost a week, and 1 had a paralytic ileus, but this passed away in a very short time. Fulness in the abdomen was a common temporary complaint, but diarrhea was the chief cause of trouble and the most obstinate of all. It was present in 39 patients (approximately 38 per cent), being temporary in 30, prolonged for several months in 2 and persistent in 7.

EVALUATION OF RESULTS

In the evaluation of results we have taken great pains not to be too enthusiastic; yet in spite of ourselves, we cannot help being greatly pleased. Nine patients have left Chicago, cannot be traced by letter and therefore are labeled "lost." That leaves 92 on whom we have definite information. A result has been classified as good when the patient is clinically well, has no ulcer symptoms, is able to eat a regular diet, takes no medicine, has no bleeding, is able to work, is holding or gaining weight and is well satisfied with his operation. A fair result is one in which the patient is still bothered by some minor trouble, such as fulness after meals, frequent belching or occasional mild episodes of diarrhea. A poor result exists when ulcer symptoms have recurred, there have been a return of bleeding, persistent diarrhea and loss of weight and the patient is unhappy about his operation. We regret to say that we do not have too much confidence in our laboratory tests even though we employ them in the majority of our cases. It has been proved by Dragstedt and others, both experimentally and clinically, that the night gastric secretions in patients with ulcer is reduced in volume and degree of acidity when vagotomy is complete; yet we have found wide variation in figures on successive determinations in the same

patient, and we believe that the average of several tests at best gives only a rough estimate of the true values. As far as the insulin test is concerned, we use it almost routinely, yet we share the opinion expressed by Paulson and Gadsden of Baltimore that the reports are often difficult of interpretation, are of questionable value in the presence of a gastroenterostomy and too frequently are positive when all clinical observations and roentgenologic evidence indicate that the result of the operation is good.

RESULTS

There have been no deaths and not one serious complication. Transthoracic vagotomy was performed in 29 cases. In 24 of these, there was no obstruction and the results were as follows: Of 17 cases of duodenal ulcer there were good results in 9, fair in 1 and poor in 1 (6 patients in this group could not be traced and therefore are listed as "lost."); of 6

TABLE 1.—*Results of Transthoracic Vagotomy (29 Cases)* *

Without Obstruction Duodenal Ulcer (17 Cases)		With Obstruction Duodenal Ulcer (2 Cases)	
Results	No. of Cases	Results	No. of Cases
Good	9	Good	2
Fair	1	(both after a long siege of diarrhea)	
Poor	1		
Lost	6		
Gastrojejunal Ulcer (6 Cases)		**Gastrojejunal Ulcer (2 Cases)**	
Results	No. of Cases	Results	No. of Cases
Good	6	Good	0
Fair	0	Fair	1
Poor	0	Poor	1
Gastric and Duodenal Ulcer (1 Case) Results, good			

* In 1 patient a transthoracic vagotomy followed a gastroenterostomy for chronic duodenal ulcer with obstruction; the result was good. There were no deaths.

cases of gastrojejunal ulcer there were good results in all, and in a patient with combined gastric and duodenal ulcer there was a good result. There was obstruction in 4 of the 29, and the results, as one would expect, were not too encouraging. Two patients had duodenal ulcers, and results in both, after a long stormy course, finally were classed as good. Two patients had gastrojejunal ulcers, in 1 the result was fair and in 1 distinctly poor (table 1).

Abdominal vagotomy was performed in 72 patients. It was performed alone, i. e., without gastroenterostomy, in 16 (none of whom had obstruction) with the following results: In 14 cases of duodenal ulcer there were good results in 9, fair in 3 and poor results in none ("lost" 2); in 1 case of gastrojejunal ulcer there was a fair result, and in 1 case of combined gastric and duodenal ulcer there was a good result (table 2).

Abdominal vagotomy was combined with a gastroenterostomy in 56 patients. Of these there were 25 without obstruction, 22 of whom had

duodenal ulcer with good results in 17, fair in 4 and poor results in none. Three of the 25 had gastric ulcer, with good results in 1 and fair results in 2. Obstruction was present in 31 of this group (all having duodenal ulcer), and the results were good in 29, fair in 1 and poor in 1 (table 3).

It is worth while, we believe, to narrate the details of the 3 cases in which the results were poor.

REPORT OF CASES

CASE 1.—Mr. B., age 29, had transthoracic vagotomy June 26, 1946, for chronic duodenal ulcer of four years' duration without obstruction. The postoperative course was good. At the end of twenty months he complained of foul eructations and was taking "amphojel" (a colloidal suspension of aluminum hydroxide)

TABLE 2.—*Results of Abdominal Vagotomy Alone (16 Patients, All Without Obstruction)*

Duodenal Ulcer (14 Cases)		Gastrojejunal Ulcer (1 Case)		Gastric and Duodenal Ulcer (1 Case)
Results	No. of Cases	Results	No. of Cases	Good
Good (2 of which needed gastroenterostomy later)	9	Good	0	
Fair	3	Fair	1	
Poor	0	Poor	0	
Lost	2			

TABLE 3.—*Results of Abdominal Vagotomy Combined With Gastroenterostomy (56 Cases)*

Without Obstruction (25 Cases) Duodenal Ulcer (22 Cases)		With Obstruction (31 Cases) Duodenal Ulcer (31 Cases)		Gastric Ulcer (3 Cases)	
Results	No. of Cases	Results	No. of Cases	Results	No. of Cases
Good	17	Good	29	Good	1
Fair	4	Fair	1	Fair	2
Poor	0	Poor	1	Poor	0
Lost	1				

for distress. The reaction to the insulin test was positive. It seems evident that the surgeon failed to divide all of the vagus fibers.

CASE 2.—Mr. C., age 52, had a chronic duodenal ulcer for twenty-nine years, with many episodes of severe hemorrhage. Gastroenterostomy was performed in 1923, after which a stoma ulcer developed and bleeding continued. Gastric resection was done in 1925, followed by more bleeding and distress. Transthoracic vagotomy was done Jan. 24, 1947, after which he continued to bleed and have pain. Gastric resection on December 20 was followed by improvement. There had been one episode of bleeding to the date of reporting.

CASE 3.—Mr. T., age 43, had chronic duodenal ulcer for fifteen years. Combined abdominal vagotomy and gastroenterostomy were performed July 1, 1947. He did well for four months, then returned with pain in the left lower part of the abdomen. Fluoroscopy showed stoma ulcer. The reaction to the insulin test was mildly positive. Medical treatment gave comfort to the patient.

COMMENT

If we include in the percentages the 9 patients whom we have designated as "lost," our results are as follows:

Total vagotomies 101

Good results	76 (75%)
Fair results	13 (12%)
Poor results	3 (2.9%)
Lost results	9

If we exclude the 9 "lost" patients from the percentages, the results would be:

Total vagotomies 92

Good results	76 (82%)
Fair results	13 (14%)
Poor results	3 (3.2%)

CONCLUSIONS

In the light of these facts it seems reasonable to conclude that vagus nerve resection, in properly selected cases, has a definite place in the surgical treatment of patients with chronic peptic ulcer who have failed to respond to medical therapy. It allows the surgeon an opportunity to choose between a dependable operation, i. e., gastric resection (which, however, carries a certain unavoidable incidence of mortality) and a less hazardous and simpler procedure which seems at the present moment to offer approximately an equal chance of good results.

DISCUSSION

OF PAPERS BY DR. RICHARD G. JACKSON AND BY DRS. EDWIN MILLER AND JOHN OLWIN

DR. LESTER R. DRAGSTEDT, Chicago: I am persuaded that the beneficial effect of section of the vagus nerves in the treatment of peptic ulcer is due to the removal of the secretory fibers in the vagi to the stomach and also in part to an interference with the motor fibers to the stomach. However, in the operation my colleagues and I employed the vagus innervation of the liver, gallbladder and pancreas is also destroyed. I shall be interested to follow the results secured by Dr. Jackson and his associates because the operation which they suggest I think is sound from the physiologic and the pathogenetic points of view of the disease. I must confess, however, that I am apprehensive about the results that they will secure. The chief difficulty, I believe, in vagus section for peptic ulcer lies in an incomplete section of the nerves to the stomach. I think that this is much more likely to be a cause of dissatisfaction with the operation than are the side effects on other abdominal viscera. For the most part these have proved to be temporary and inconsequential. The body adjusts itself so that no serious disturbance is seen after a period of three or six months. On the other hand, we have learned both from work on patients and work on lower animals that to obliterate the nervous phase of gastric secretion all of the vagus fibers to the stomach have to be divided. The results obtained by Dr. Miller and Dr. Olwin following this operation are most nearly in accord with those that we have seen. I feel convinced that when surgeons become more familiar with the operative technic and more familiar with postoperative therapy and the complications that may be expected the results with this method of treatment will steadily improve. The situation here, I suspect

will be like that experienced with subtotal resection in the treatment of ulcers. The results following this procedure now are better and the mortality rate is less than when the operation was first introduced.

Dr. John M. Dorsey, Chicago: I have been interested in the statistical data that Drs. Miller and Olwin have presented because, in the first place, I have operated on, at the Presbyterian Hospital, a number of the patients included. In the second place, as surgeon with a duodenal ulcer of my own and a possible candidate for surgical treatment, I have not been unfavorably impressed by the clinical results arrived at in the study of these patients. Certainly the exact place for vagotomy in the surgical treatment of ulcer is being carefully evaluated through the medium of this study and studies made following Dragstedt's primary work.

There is another indication for vagotomy to which I should like to call attention, and that is in connection with the repair of the esophageal hiatus type of diaphragmatic hernia. Some time ago Dr. N. C. Gilbert of Chicago became interested in the frequent association of duodenal ulcer and other upper abdominal pathologic lesions with this type of diaphragmatic hernia. It was his impression that reflex stimulation of the vagus fibers caused by these upper abdominal lesions might be a factor in the production of diaphragmatic hernia through their effect of shortening the esophagus through the action of the stimulated vagus nerve. Using the dog as an experimental animal and avoiding drugs which inhibit vagal impulses, he was able to show that direct and indirect stimulation of the vagus produced contraction and shortening of the esophagus and, in so doing, caused the stomach to be sharply drawn up into the thoracic cavity. Dr. Carl Davis Jr. and I have repeated to our satisfaction the work of Dr. Gilbert in the experimental animal. However, direct stimulation by crushing of the severed distal vagus segment of the nerve in the human being did not cause apparent contraction of the esophagus or upward motion of the stomach. It should be stated in this regard, however, that these patients so tested did have preliminary preoperative medication, which, in the experimental animal, would have eliminated the vagal effect. Scrimger's experiments in the dog have shown that division of both vagus nerves has caused a decided lengthening and some tortuosity of the esophagus.

It seemed reasonable to us that patients with diaphragmatic hernia who were also having symptoms distinctly referable to a proved duodenal ulcer would be suitable candidates for repair of the diaphragmatic hernia in the prescribed fashion plus bilateral division of the vagus nerve. We have carried this out in 2 patients with satisfactory results from the point of view both of their diaphragmatic hernia repair and of their duodenal ulcers. These patients will be reported on at a later date.

Dr. Waltman Walters, Rochester, Minn.: It is a pleasure to participate in the discussion of the papers presented by Dr. Jackson and by Drs. Miller and Olwin.

I think that Dr. Jackson has made a fine contribution to the anatomic studies of the vagus nerves and their termination in the stomach, and I, too, shall look forward with the greatest interest to see his contrasting results in this group of cases in which the various branches of the vagi are divided at their lower ends close to the stomach.

Last year before this society, as participants in a symposium on vagotomy in the treatment of peptic ulcer, my assistants and I presented the results of our anatomic studies made on 56 men, 44 women and 11 children during the course of postmortem examinations.

These anatomic studies indicated that the gastric nerves could be located and successfully resected near the diaphragm by either a transabdominal or a transthoracic approach in approximately 92 per cent of the cases and that possibly most, if not all, of the branches in the remaining 8 per cent also could be located in the same way.

I was greatly interested in Dr. Miller and Dr. Olwin's exposition on the results in the treatment of peptic ulcer by vagus nerve resection; such presentations, in which the results in cases in various categories are shown, make comparisons in various reported groups of cases possible and thereby permit sound conclusions to be drawn. The American Gastro-Enterological Association has such a comparative study under way at the present time. It is worth emphasizing, as they did in their final statement, that excellent results were obtained in from 75 to 80 per cent of their reported cases. That, in general, has been the experience at the Mayo Clinic in 177 cases in which vagotomy was done alone or along with additional drainage operations on the stomach, such as gastroenterostomy, pyloroplasty and partial gastrectomy. The employment of vagotomy alone in the treatment of 26 of my patients with duodenal ulcer gave excellent results in only 65 per cent of cases. When it is used in the treatment of recurring ulcer after partial gastrectomy, I think that it is an operation of great merit, probably unexcelled by any other surgical procedure. Of 29 such cases in which the operations were performed by my colleagues and myself, excellent results were obtained in 88 per cent.

With the help of some of my assistants I have recently studied 177 cases in which vagotomy was performed at the clinic; 77 of the patients were operated on by myself and 100 by my colleagues. The cases in which vagotomy alone is done should be evaluated most carefully, for the good results associated with gastroenterostomy, or partial gastrectomy, or partial gastrectomy in the absence of vagotomy, and the physiochemical changes resulting from dilution, reduction and neutralization of gastric acidity prevent evaluation of the effects of vagotomy. If I remember correctly, there were 29 cases in this category in which there were two recurrences of ulcer, an incidence of approximately 7 per cent.

I have proved that ulcer recurred in 5 (6.5 per cent) of my total of 77 cases in which vagotomy alone or in association with an additional gastric operation was performed. In 4 of these cases the results of insulin tests were negative. In addition, recurrence of ulcer has been suspected, on the basis of return of ulcer symptoms, in 9 other cases (11.7 per cent) of the 77 in which I operated. The suspected recurrences were not proved, however, by examination. Of the 8 cases in which insulin tests were done, in 6 the results were negative.

I should like to emphasize again, as I did on a previous occasion, that either the Hollander insulin test does not always indicate the completeness of the vagus nerve resection or a complete resection of the vagus nerves is not necessary to obtain results that are comparable to those obtained in the group in which the results of the test are negative. It has been assumed by Dragstedt than an insulin-positive reaction is an indication of incompleteness of the nerve resection. In my experience the results as measured by relief of ulcer pain have been practically the same in both groups. Troublesome disturbance of motility has occurred in about the same percentage in both groups, and both groups have had corresponding reduction of gastric acidity, but, curiously enough, in my cases of proved recurrence all the reactions to insulin were negative.

I am in accord with Dr. Dragstedt and Dr. Miller that there is a definite place for vagus nerve resection. It is definitely indicated in cases of recurring ulcer after partial gastrectomy and in many cases of recurring ulceration after

gastroenterostomy. Resection of the vagus nerve is seldom indicated in cases of gastric ulcer (except in those cases in which the ulcer is difficult and dangerous to remove [which is seldom the case] and in which there is at least a 20 per cent possibility that the lesion may be malignant) and should, of course, be removed. Vagotomy is seldom indicated in cases of duodenal ulcer in which gastroenterostomy, pyloroplasty or partial gastrectomy is not to be performed. If only resection of the vagus nerves is carried out, many patients have such persistent troublesome gastric motility disturbances that an additional drainage operation on the stomach frequently becomes necessary; this is especially true if selectivity of patients for operation is such that as few as 14 per cent of all patients with ulcers who are encountered are operated on.

In 1 of my patients a large perforating gastrojejunal ulcer developed after an anterior gastroenterostomy and a vagotomy. It was necessary to do a jejuno-jejunostomy twenty-six days after these procedures had been carried out, because of serious persisting gastric and jejunal retention. The results of the insulin test were persistently negative. Partial gastrectomy later removed the ulcer and relieved all of the symptoms. Unsatisfactory were the results also in 2 of 7 cases of gastrojejunal ulceration in which, after vagotomy, removal of the gastro-enteric stoma and restoration of gastrointestinal continuity, recurring duodenal ulcer craters were visualized roentgenographically. The results of the insulin test were positive in 1 of these cases and negative in the other.

EVALUATION OF CONSERVATIVE RESECTION

With End to End Anastomosis for Carcinoma of the Rectum and Lower Sigmoid Colon

JESSIE GRAY, M.D.
TORONTO, CANADA

THIS PAPER is not a crusade for resection of the rectum with restoration of continuity. It is an honest endeavor to assess the place of conservative resection, if any, in the operative therapy of rectal carcinoma. Certain facts are presented, and certain conclusions are drawn. Facts cannot be questioned, but conclusions should be critically assessed.

There are two basic arguments against anterior resection with end to end anastomosis as a means of dealing with carcinomas of the rectosigmoid and upper part of the rectum. One might be termed anatomic: the question of the blood supply of the upper end of the rectal stump after division of the superior hemorrhoidal artery. It has been established beyond question that, if the resection is carried down to the level of the levator ani muscles, the rectum distal to this has a perfectly adequate blood supply apart from the superior hemorrhoidal artery. One cannot, of course, divide the superior hemorrhoidal artery and then leave a long avascular stump of rectum proximal to the levators. The resection must remove the entire rectum to the level of the levator muscles.

The other argument against conservative resection with restoration of continuity might be called the pathologic one: the question of whether or not metastases may occur in a downward direction from these tumors. The anatomic studies of Coller [1] and of Gilchrist [2] of the lymphatic spread of carcinoma of this region indicate that the great mass of tissue resected need only be upward from the tumor. In Gilchrist's latest paper, of two hundred cleared specimens only seven showed involvement of lymphatic glands distal to the tumor. These seven were all advanced cases in which the lymphatic glands above were completely blocked by carcinoma, allowing retrograde permeation

Read at the Fifth Annual Meeting of the Central Surgical Association, Feb. 20, 1948.

1. Coller, F. A.; Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastasis of Carcinoma of Rectum, Surgery **8**:294, 1940.

2. Gilchrist, R. K., and David, V. C.: Lymphatic Spread of Carcinoma of the Rectum, Ann. Surg. **108**:621, 1938.

downward. The lowest node in these specimens was 4 cm. below the lower edge of the tumor. This throws doubt on the necessity for an abdominoperineal excision of all carcinomas of the lower part of the sigmoid colon and upper part of the rectum. Just as radical a removal of the tumor with the perirectal and pelvic gland-bearing area can be obained by anterior resection with end to end anastomosis as by total extirpation of the rectum.

The technical procedure as such of conservative resection of the rectum presents no barrier or difficulty, but this question should not be given any great commendation merely because of successful technic. So often an operation has been commended because of an author's pride in the fact that he has made a difficult operation mechanically safe by his technical procedure. Gilchrist [3] put it well when he said that the real question is "Can you remove all the cancer?" and not "Can you sew two ends of bowel together?" It must be understood that anterior resection of the rectum with restoration of continuity for carcinoma is not advocated merely because a technical procedure has been devised which makes it mechanically possible and safe.

MATERIAL

This study covers a period from 1939 to 1946, during which a group of 74 public and private patients were subjected to conservative resection with end to end anastomosis for carcinomas situated within an anatomic level range where many persons would consider anything but an abdominoperineal resection inadequate. By comparison of the results in these 74 cases with those reported in the literature for abdominoperineal resection of tumors within the same level range it is hoped that the question may be answered as to whether conservative resection with restoration of continuity is, in some circumstances, as adequate an operation as total extirpation of the rectum.

RESULTS

Of the 74 patients, 3 died of the operative procedures. This operative mortality rate of 4 per cent is not forbidding when consideration is given to the fact that the resectablity rate was over 90 per cent of patients who underwent exploration.

Table 1 shows the relationship of results to the stage of the disease as based on Duke's classification. It confirms what has been shown repeatedly in the literature, namely, that the percentage survival rate is in inverse relation to the stage of the disease. Eighty per cent of the patients with stage I carcinomas were alive and well at the time of reporting. Over 56 per cent of those with carcinomas of stage II

3. Gilchrist, R. K., and David, V. C.: Prognosis in Carcinoma of the Bowel, Surg., Gynec. & Obst. **86**:359 (March) 1948.

and III have survived. In the stage IV group the number alive and well drops precipitously to 25 per cent.

Table 2 shows that glandular secondary involvement is of prognostic significance so far as 57 per cent of patients with no gland involvement were alive and well at the time of writing whereas only 39 per cent of those with gland involvement have survived.

From the point of view of comparing the results of conservative resection with those of total extirpation, the relationship of results to the anatomic level of the tumor in the bowel is of greater interest than

TABLE 1.—*Relation of Results to Stage of Disease (Duke's) in 74 Cases*

Number of Cases	Percentage	Stage	Alive and Well	Alive with Recurrence
5.....	7	I	4 (80% of 5)	0
32.....	43	II	19 (59% of 32)	0
21.....	28	III	11 (52% of 21)	1 (5% of 21)
16.....	22	IV	4 (25% of 16)	0

TABLE 2.—*Relation of Results to Gland Involvement in 74 Cases*

Number of Cases	Percentage	Glands	Alive and Well	Alive with Recurrence
51.....	68	Not involved	29 (57% of 51)	1 (2% of 51)
23.....	32	Involved	9 (39% of 23)	0

TABLE 3.—*Relation of Results to Level of Tumor in 74 Cases*

No. of Cases	Per-centage	Level	Alive and Well	Alive with Recurrence
12.....	16	Below peritoneum	2 (17% of 12)	1 (8% of 12)
30.....	41	Upper part of rectum	22 (73% of 30)	0
18.....	24	Rectosigmoid	6 (33% of 18)	0
14.....	19	Lower part of sigmoid	8 (57% of 14)	0

the relationship to either stage of disease or gland involvement. The cases were divided on the basis of anatomic level into four groups: (1) below the bottom of the pouch of Douglas, (2) upper part of the rectum, that is, between the bottom of the pouch of Douglas and the rectosigmoid junction, (3) rectosigmoid and (4) lower part of the sigmoid colon.

The relationship of results to level of growth is shown in table 3. It will be observed that the percentage of patients alive and well rises as the level of the tumor proceeds proximally with the exception of the high incidence of survivals among patients whose growths were of the upper rectal level. It is of distinct concern that only 17 per cent

of those patients whose tumors were below the bottom of the pouch of Douglas were alive and well after conservative resection. The good results in the group with tumors in the lower sigmoid level are undoubtedly to be expected. To understand why the results in the group with tumors of the upper rectal level so excel those with tumors of the rectosigmoid and even the lower sigmoid level some account must be taken of stage of disease and gland involvement.

An attempt has been made to do this by dividing the cases arbitrarily into two groups on the basis of stage and gland involvement. The first group is the one in which the prognosis should be good and consists of all cases of stage I and stage II carcinomas, whether or not glands were involved, and those stage III tumors in which there was no gland involvement. The second group is the one in which the prognosis should be poor and consists of all cases of stage IV growths, whether or not glands were involved, and those stage III carcinomas in

TABLE 4.—*Data in Cases in Each Group Defined*

Level	Number of Cases	Good Prognosis, Stages I and II and Stage III Without Glandular Involvement	Alive and Well	Poor Prognosis, Stage IV and Stage III with Glandular Involvement
Below peritoneum.....	12	10 (83% of 12)	2 (17% of 12)	2 (17% of 12)
Upper part of rectum..	30	23 (77% of 30)	22 (73% of 30)	7 (23% of 30)
Rectosigmoid	18	7 (39% of 18)	6 (33% of 18)	11 (61% of 18)
Lower part of sigmoid	14	11 (78½% of 14)	8 (57% of 14)	3 (21½% of 14)

which there was gland involvement. Table 4 shows the number in each level group which fall into each of these two groups defined.

From table 4 it is seen that the low percentage (17 per cent) of the patients with lesions below the peritoneum level that were alive and well at the time of writing is of even deeper concern in view of the fact that 83 per cent of these patients fall into the group which should have a good prognosis on the basis of stage and gland involvement. It is possible, of course, that involved glands are not found along the surface of the levator ani in this low level group in as large a proportion of the instances in which they are present as are found among the mesenteric glands in the more proximally situated tumors. To find involved lymph glands Gilchrist cleared his specimens with a fat solvent which leaves the carcinoma-containing lymph glands standing out in relief. My co-workers and I have not cleared our specimens and consequently may often miss involved glands, particularly in the very low-lying growths. The 57 per cent that were alive and well among the patients with low sigmoid level tumors is not especially remarkable in view of the fact that 78.5 per cent of these patients fall into the

group that should have a good prognosis on the basis of stage and gland involvement. That a larger percentage (73 per cent) of the patients with upper rectal level lesions have survived than of the patients with rectosigmoid level lesions (33 per cent) is undoubtedly due to the fact that 77 per cent of the former fall into the group which should have a good prognosis as based on stage and gland involvement, whereas only 39 per cent of the patients with rectosigmoid lesions are in the same favorable group. I attribute the better prognosis on the basis of stage and gland involvement of the growths of upper rectal level to the anatomic fact that this portion of the bowel is relatively avascular in comparison with the rest of the rectum and colon. Consequently carcinomas of the upper part of the rectum have a scantier blood supply on which to grow and fewer lymphatic channels along which they can metatasize in comparison with the relatively profuse blood supply and lymphatic drainage available to carcinomas below the peritoneum and the rectosigmoid.

In regard to how low in the rectum a growth may be and still allow of resection with restoration of continuity, a good working rule is to hesitate if the tumor is readily palpable on digital rectal examination, because most of these lie below the peritoneum for which the results of conservative resection have been poor. However, the gross pathologic type of the carcinoma may influence one in this decision. If it is a tumor of the polypoid type without fixation it is usually of relatively low grade malignancy, and it may be justifiable to consider conservative resection in such a case irrespective of the size of the polypoid growth. On the other hand, sessile ulcerated scirrhous infiltrating carcinomas are much more malignant, and even though small, if such a growth can be reached digitally per rectum, the patient should probably be subjected to total extirpation of the rectum.

It must, of course, be remembered that palpability of a tumor on digital rectal examination depends not only on the actual level of the growth but also on such factors as the length of the examiner's finger, the obesity of the patient, the gross pathologic type of the carcinoma and the position in which the patient is examined. I have found that where a tumor is suspected but not felt on ordinary rectal examination, it often becomes palpable in examination of the patient in the erect position. No definite rule may be set down, but from the relatively poor results of conservative resection in patients whose growths occur below the bottom of the pouch of Douglas it may be stated that, unless the carcinoma is definitely polypoid in type and freely movable, resection with restoration of continuity should not be undertaken when the tumor is readily within reach of the examining finger.

Among the entire 74 cases there have been 18 instances of local recurrence of disease. Four of these followed resections which were

palliative because of the tremendous local extent of the growth. Hence there have been 14 local recurrences in 70 resections in which the local extent of the tumor permitted what appeared to be complete and satisfactory removal of the local lesion. Of the 14 patients in whom there was local recurrence 12 died, 1 was alive and well following an abdominoperineal resection of the recurrence and 1 was alive having had a palliative colostomy for obstruction. An attempt has been made to relate the development of local recurrence of carcinoma to the stage of disease, whether or not glands have been involved, and the anatomic level of the tumor. This has been done by comparing the percentage incidence of each stage, at each level and with reference to gland involvement of the local recurrences with that of the whole group of 74 cases. This analysis and comparison are shown in table 5.

TABLE 5.—*Comparison of Incidence of Recurrence in Each Stage in 14 Cases with Total Series*

	Number of Local Recurrences	Percentage of Local Recurrences	Percentage of All 74 Cases	Number of All 74 Cases
Stage				
I	0	0	7	5
II	6	43	43	32
III	5	36	28	21
IV	3	21	22	16
Glandular Involvement				
With	5	36	32	23
Without	9	64	68	51
Level				
Below peritoneum	6	43	16	12
Upper part of rectum	4	28.5	41	30
Rectosigmoid	2	14.25	24	18
Lower part of sigmoid	2	14.25	19	14

In table 5 it will be observed that, of the middle two columns, the left shows the percentage of the local recurrences in which the tumors were (1) of the various stages, (2) with and without gland involvement and (3) at the various anatomic levels in the bowel. The right of the middle two columns shows the percentage of the entire series in which the tumors were (1) of the various stages, (2) with and without gland involvement and (3) at the various anatomic levels. It is seen that these two columns parallel one another fairly closely in reference to (1) the stages of disease and (2) gland involvement. Because of this it is concluded that the development of local recurrence of carcinoma does not depend particularly on the stage of the disease as based on Duke's classification or on whether or not there has been involvement of the regional lymphatic glands. But there is no similarity between the middle two columns in reference to (3) the anatomic levels of the growths. Therefore it is apparent that the development of local recurrence of disease does depend to a high degree on the anatomic level of the carcinoma in the bowel. Forty-three per cent of the local recurrences

occurred in cases in which the growth was below the peritoneum in level, and tumors at this level comprise only 16 per cent of the entire series.

It is assumed arbitrarily that those 4 cases of local recurrence in which the growths were at the rectosigmoid or low sigmoid colon level could not have been prevented by abdominoperineal resection, because the latter would not be more radical than conservative resection of tumors at this high level in view of the evidence submitted of the direction of lymphatic spread. Of the remaining 10 cases of local recurrence in which the carcinoma occurred in the rectum proper, 3 fall into the group the prognosis for which would be expected to be poor anyway as the carcinomas were stage IV or stage III with gland involvement. Therefore there are 7 cases of local recurrence of rectal growths in which the prognosis should have been good, as the tumors were stage I or II or stage III without gland involvement. Of the 7 patients, 5 had carcinomas of below peritoneum level. Therefore, if conservative resection with restoration of continuity had been reserved for those patients whose growths were above the bottom of the pouch of Douglas, it would seem that in this series, if one takes into consideration the level of the tumor, stage and incidence of gland involvement, there were only 2 patients with local recurrence which might conceivably have been avoided by total extirpation of the rectum.

Subtracting the 12 cases of below peritoneum level carcinomas from the total series of 74, one has left 62 in which growths occurred above the bottom of the pouch of Douglas. An incidence of 2 cases of local occurrence which might have been prevented by total extirpation among 62 cases of above peritoneum level tumors comprises a 3 per cent incidence of avoidable recurrences resulting from conservative resection. Because of the poor results of anterior resection for carcinomas which arise below the bottom of the pouch of Douglas it is concluded that resection with restoration of continuity should be reserved for patients whose growths occur above the peritoneum. It may be that the obviation of a permanent colostomy warrants the 3 per cent increase of risk of failure to cure the patient of cancer which is incurred when conservative resection with end to end anastomosis is carried out on patients whose tumors lie above the bottom of the pouch of Douglas.

In the entire series of 74 cases there were 8 palliative resections, 3 postoperative deaths and 4 deaths from intercurrent disease. If these 15 case are deleted, 59 patients are left who were operated on for cure and who have not died of operation or of intercurrent disease, that is, have not died of noncarcinomatous causes. Table 6 shows the results in these 59 cases broken down on the basis of the time interval between their resections and September 1947.

From tables 6 and 7 it is seen that, while 79 per cent of the patients operated on between two and five years prior to reporting were alive

and well, only 42 per cent of those with resection over five years prior to writing survived. From this it might be concluded that a number of patients must have died of recurrent carcinoma three, four and five or more years after operation in order to make the survival rate drop from 79 per cent to 42 per cent; but when all 20 deaths from recurrent carcinoma are analyzed on the basis of survival time, it is found that 13 patients died within two years of resection and only 7 lived more than two years, that is, 13 out of 20, or 65 per cent of deaths from recurrent carcinoma, occurred within two years of operation. If 65 per cent of the deaths from recurrent disease occur within two years of resection, then the higher (79 per cent) survival rate observed among the cases with more recent resection may be due to improvement in the entire management of these patients of recent years. The 19 patients operated on between two and five years previously have already been followed

TABLE 6.—*Summary of Data with Respect to Survival*

Number of Years Since Resection	Number of Cases	Alive and Well	Alive with Recurrence	Dead
Over 5	24	10 (42% of 24)	0	14
2-5	19	15 (79% of 19)	1	3
Under 2	16	13 (81% of 16)	0	3

TABLE 7.—*Analysis of 20 Deaths*

	Dead in Less Than 1 Yr.	Dead in 1-2 Yr.	Dead After 2 Yr.
Number of cases	3	10	7
Cumulative number	3	13	20
Cumulative percentage	15	65	100

for the crucial initial first two year period during which 65 per cent of the deaths from recurrent carcinoma occur; yet 15, or 79 per cent, of them were still alive and well. Hence it is concluded that the percentage of so-called five year cures will be much higher than 42 per cent among the patients with more recent resection as they pass the five year milestone.

It is recognized that the numbers as presented in table 6 are much too small to yield conclusions which are statistically sound and that the deductions drawn are more in the nature of interesting speculations rather than actual valid conclusions. Nevertheless these figures show a trend which permits optimism.

ANALYSIS OF DEATHS

Certain points of interest arose from a study of the total 35 deaths among the entire series of 74 cases. The analysis of these deaths is presented in table 8.

Three deaths occurred in the immediate postoperative period: 1 of pneumonia, 1 due to a technical error resulting in defective blood supply to the upper stump of sigmoid with leak from the anastomosis and fatal peritonitis and the third three weeks after the palliative resection of a huge growth which proved literally to be inoperable.

Eight deaths followed the remaining palliative resections. Four of these resections were palliative because of the local extent of the disease, and the average survival time of these patients was nine months. The other four resections were palliative because of the presence of secondary involvement in the liver at the time of operation, and these patients survived an average of sixteen months. It is surely worth while to prolong a man's life a year or more by palliative resection, particularly in view of the fact that the resection does not contribute to his ultimate

TABLE 8.—*Analysis of Total 35 Deaths*

Number of Cases	Cause of Death		Average Survival Time
3	Postoperative		14 days
8	Resections palliative	because of local extent (4 cases)	9 mo.
		because of liver metastases (4 cases)	16 mo.
4	Intercurrent disease	Cerebral accident (1 case)	6 mo.
		Old age and inanition (1 case)	3 mo.
		Coronary thrombosis (2 cases)	2 yr., 10 mo.
20	Recurrent carcinoma	Distant metastases (5 cases)	3¾ yr.
		Retroperitoneal glands (2 cases)	3½ yr.
		Generalized peritoneal (1 case)	2½ yr.
		Local recurrence (12 cases)	Almost 2 yr.

death and during his remaining span of life he is relieved of the distress of the persistent primary growth.

Four deaths were due to intercurrent disease: 2 from coronary occlusion, twenty-one months and almost four years after resection, 1 from a cerebral accident six months after operation and 1 from simple old age and inanition within a few weeks of the patient's discharge from hospital.

The remaining 20 deaths were due to recurrent carcinoma. Five patients died of distant metastases from fourteen months to over eight years after operation, averaging three and three-quarters years' survival. In 2 patients there developed recurrence in retroperitoneal glands, in one almost two years and in the other almost five years after resection. Generalized peritoneal metastases appeared in 1 patient and resulted in death two and a half years after operation. In 12 patients there developed local recurrences, with an average survival time of almost two years.

Of all the deaths, it is assumed that those which were postoperative, after palliative resection, of intercurrent disease or of distant metastases would have occurred no matter what type of resection had been performed. The remaining 15 deaths from recurrent carcinoma in the retroperitoneal glands, studded throughout the peritoneal cavity or local at the site of the original tumor, are the ones which are debatable in reference to the type of operation to which the patient was subjected. Table 9 presents the analysis of these 15 debatable deaths, subdivided as to anatomic level of tumor and also as to prognosis as based on stage and gland involvement of the growth.

It is assumed, in view of the extent of the dissection above the level of the levators in conservative resection and the evidence regarding the direction of lymphatic spread of carcinoma in this region, that the 5 deaths of patients whose tumors were at rectosigmoid level or higher could not have been prevented by abdominoperineal resection of the

TABLE 9.—*Analysis of 15 Debatable Deaths*

Level	Number of Cases	Good Prognosis, Stages I and II and Stage III Without Glandular Involvement	Poor Prognosis, Stage IV and Stage III with Glandular Involvement
Below peritoneum	6	5	1
Upper part of rectum	4	2	2
Rectosigmoid	2	0	2
Lower part of sigmoid	3	3	0

entire rectum. If one deletes those 3 cases in which prognosis was poor anyway, as gaged by extent and gland involvement of the growths, from the remaining 10 cases in which carcinomas arose in the rectum proper, there are left 7 deaths among patients who should have had a good prognosis. Of these 7, 5 had tumors below the bottom of the pouch of Douglas. In the light of this study it now seems that these 5 patients should have had total extirpation of the rectum. Had conservative resection with restoration of continuity been reserved for the total of 62 patients whose growths were above the peritoneum, there should have been only 2 deaths, which, because of the level, stage and gland involvement of the carcinomas, might conceivably have been prevented by abdominoperineal excision.

SUMMARY

Seventy-four cases of conservative resection with end to end anastomosis for carcinoma of the rectum and rectosigmoid region are reviewed. The operative mortality rate among these patients was 4 per cent. The expected relationship of survival to stage of disease has

been confirmed. Eighty per cent of the group with stage I carcinoma were alive and well, 52 to 59 per cent of the groups with stages II and III carcinomas have survived and only 25 per cent of the group with stage IV carcinomas were alive and well at the time of writing.

The expected relationship of survival to gland involvement has been confirmed. Fifty-seven per cent of patients without secondary involvement in glands were alive and well, while only 39 per cent of those with gland involvement have survived.

Results of conservative resection are found to be related to the anatomic level of the tumor in the bowel. Only 17 per cent of the patients whose growths arose below the bottom of the pouch of Douglas have survived. The percentage survival of patients with carcinomas at other levels is found to depend on the stage and gland involvement of the tumor. The highest percentage of good results is obtained in growths of upper rectal level. This is attributed to the relative avascularity of this portion of the bowel with resultant slower growth and spread of carcinomas arising at this level.

Unless a carcinoma is definitely polypoid in type and freely movable, resection with preservation of the anal canal should not be undertaken when the growth is readily within reach of the examining finger per rectum.

The development of local recurrence of disease is found to have no special relationship to stage of disease or gland involvement but a distinct relationship to anatomic level of the tumor in the bowel. Forty-three per cent of the local recurrences have occurred among the patients with carcinomas below the peritoneum, which comprise only 16 per cent of the entire series.

If conservative resection had been reserved for patients whose carcinomas were above the peritoneum, only 3 per cent would have had recurrences which might conceivably have been avoided by total extirpation of the rectum.

Eighty per cent of patients operated on within the five years prior to writing were alive and well as compared with only 42 per cent of those with resection done more than five years previously. Evidence is brought forth to support the belief that this is due in large part to improved management of recent years. A higher percentage of "five year cures" is to be expected in the future, particularly if conservative resection is reserved for tumors above the peritoneum.

All of the deaths in the entire series are analyzed as to cause, survival time and debatability in reference to the type of operation performed. Among 62 patients with growths above the peritoneum, conservative resection resulted in only 2 deaths which, because of the level, stage and gland involvement of the carcinomas, might conceivably have been prevented by abdominoperineal resection.

CONCLUSIONS

Conservative resection with end to end anastomosis for carcinoma of the rectum and rectosigmoid region results in an operative mortality rate which is not forbidding. The results in cases in which the tumor lies above the bottom of the pouch of Douglas are only 3 per cent less favorable than those which might be obtained by total extirpation of the rectum. It is submitted that the obviation of a permanent colostomy warrants the 3 per cent increase of risk of failure to cure the patient when the carcinoma occurs above the peritoneum.

The recurrence rate among patients with growths below the bottom of the pouch of Douglas who are subjected to anterior resection with end to end anastomosis is so high as to forbid this conservative resection with preservation of the anal canal in these low-lying tumors.

Much of the material on which this paper is based was obtained from the records of Dr. Roscoe R. Graham, and many of the ideas incorporated in the paper were obtained from him by personal communication. Dr. F. I. Lewis and Dr. J. R. F. Mills gave permission for the inclusion of some of their cases in the analysis. The operations were all performed at either the Toronto General Hospital by the aforementioned surgeons or at the Women's College Hospital by me.

SYMPATHETIC DYSTROPHY

WILLIAM D. HOLDEN, M.D.
CLEVELAND

THE SUBJECT of this paper is a term uncommonly used and poorly understood, not only by the medical profession in general but also by the physicians and surgeons interested in painful extremities. It is a term that may be rightfully discarded within a few years when a better understanding of the syndrome is obtained. For the present, however, it signifies, as well as any term, pain in an extremity that may be relieved by interruption of regional efferent sympathetic fibers. Such terms as Sudeck's atrophy, causalgia-like state, post-traumatic painful osteoporosis, reflex dystrophy of the extremities and minor causalgia have been used to designate this syndrome. Sympathetic dystrophy has been compared to causalgia. The latter term, however, refers to the syndrome first described by Mitchell, Morehouse and Keen [1] and implies a burning type of pain not confined to the distribution of a peripheral nerve and occurring after trauma to one or more of the major nerves of an extremity. In some instances of sympathetic dystrophy there are demonstrable injuries to small sensory nerves such as the digital, but many times damage to a somatic nerve cannot be inferred, let alone demonstrated. The type of pain occurring in sympathetic dystrophy varies considerably. It may be burning, aching or throbbing pain, or it may be numbness and tingling. It is my impression that sympathetic dystrophy occurs frequently in maladjusted persons, whereas causalgia occurs chiefly in healthy young men who have shown little tendency to anxiety or hypochondriasis prior to their injury. I believe that some clarification of the clinical syndromes will be obtained if the term causalgia is reserved for the burning painful syndrome that follows trauma to a major nerve of the extremity, and that sympathetic dystrophy, designated as post-traumatic, post-phlebitic, postinfectious or postarthritic, is applied to the painful states that may be relieved by sympathetic interruption.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 21, 1948.

From the Department of Surgery, Western Reserve University School of Medicine and University Hospitals.

1. Mitchell, S. W.; Morehouse, G. R., and Keen, W. W.: Gunshot Wounds and the Injuries of Nerves, Philadelphia, J. B. Lippincott & Company, 1864.

The anatomic and physiologic mechanisms playing a part in the pain of sympathetic dystrophy are obscure. Leriche,[2] Livingston,[3] Lewis,[4] de Takats,[5] Freeman[6] and Doupe[7] have made notable contributions and given considerable thought to this subject.

Animal experimentation has not been particularly fruitful in clarifying the clinical syndrome of sympathetic dystrophy. There are many reasons for this, chiefly the fact that no experimental reproduction of the syndrome has thus far been successful and also that it is hazardous to transfer to human beings the results of animal experimentation on the autonomic nervous system. On some occasions, patients who have had certain diagnostic and therapeutic studies performed have yielded a considerable amount of information about the pathophysiologic mechanisms concerned in sympathetic dystrophy.

SYMPATHETIC AFFERENTS

A concept of this syndrome that many neurovascular surgeons have entertained and have been forced to discard is that the painful impulses are transmitted by way of sympathetic pathways. During the course of procaine injections into either the stellate or lumbar ganglions, the immediate disappearance of pain in the extremity, at times before the injection is completed, suggests interruption of sensory impulses. It has been observed during stellate ganglion injections with procaine that no matter how quickly the subsidence of pain occurs, it is preceded by a miosis of the pupil. Kuntz[8] demonstrated in the cat that afferent

2. Leriche, R.: The Surgery of Pain, translated and edited by A. Young, Baltimore, Williams & Wilkins Company, 1939.

3. Livingston, W. K.: Pain Mechanisms: A Physiologic Interpretation of Causalgia and Its Related States, New York, The Macmillan Company, 1943.

4. Lewis, T.: Pain, New York, The Macmillan Company, 1942.

5. (*a*) de Takats, G.: Reflex Dystrophy of the Extremities, Arch. Surg. **34**:939 (May) 1937. (*b*) Miller, D. S., and de Takats, G.: Post Traumatic Dystrophy of the Extremities, Surg., Gynec. & Obst. **75**:558, 1942. (*c*) de Takats, G., and Miller, D. S.: Post Traumatic Dystrophy of the Extremities; A Chronic Vasodilator Mechanism, Arch. Surg. **46**:469 (April) 1943. (*d*) de Takats, G.: Nature of Painful Vasodilatation in Causalgic States, Arch. Neurol. & Psychiat. **50**:318 (Sept.) 1943; (*e*) Causalgic States in Peace and War, J. A. M. A. **128**:699 (July) 1945.

6. Freeman, N. E.: Treatment of Causalgia Arising from Gunshot Wounds of the Peripheral Nerves, Surgery **22**:68, 1947.

7. Doupe, J.; Cullen, C. H., and Chance, G. Q.: Post Traumatic Pain and the Causalgic Syndrome, J. Neurol., Neurosurg. & Psychiat. **7**:33, 1944.

8. Kuntz, A., and Farnsworth, D. I.: Distribution of Afferent Fibers via the Sympathetic Trunks and Gray Communicating Rami to the Brachial and Lumbosacral Plexuses, J. Comp. Neurol. **53**:389, 1931. Kuntz, A., and Saccomanno, G.: Afferent Conduction From Extremities Through Dorsal Root Fibers via Sympathetic Trunks, Arch. Surg. **45**:606, 1942.

impulses from the extremities traversed the sympathetic ganglions to elicit reflex changes in the pupils. He did not claim, however, to have demonstrated the transmission of painful impulses via sympathetic ganglions. Leriche [2] stated his belief that afferent impulses may be transmitted via sympathetic pathways. Threadgill [9] recently claimed to have shown in the dog that impulses enter the spinal cord through the lumbar sympathetic chains from the lower extremities. Attempts in the laboratory at Western Reserve University to reproduce his experiments have failed. The repeated clinical observation that spinal anesthesia without efferent sympathetic paralysis abolishes the pain of sympathetic dystrophy or causalgia suggests transmission of the pain through somatic nerves. A series of experiments by Moore and Singleton [10] led to the convincing conclusion that all painful impulses from the extremities passed through somatic nerves.

BLOOD FLOW

Because the interruption of sympathetic efferent impulses, either temporarily or permanently, has been so effective in treating patients with sympathetic dystrophy, attempts have been made to indict altered peripheral blood flow as the underlying pathophysiologic mechanism in this disease. It is untenable that changes in the total blood flow of an extremity, either an increase or decrease, are the basic alterations. De Takats [8b] has shown that many of the patients, especially early in the course of their disease, have an increased blood flow measured plethysmographically. It will be demonstrated subsequently that patients may have increased, normal or decreased blood flow. It is difficult to conclude in view of these observations that alterations of total blood flow are concerned etiologically with the pain of sympathetic dystrophy.

INTERNUNCIAL POOL CONCEPT

Livingston,[8] who has given a considerable amount of thought to this subject, expressed the belief that there are three factors involved in establishing a vicious circle of reflexes. He has portrayed the mechanism as being initiated by chronic irritation of a peripheral sensory nerve. The increased number of afferent impulses create an abnormal state of activity in the internuncial neuron centers, and in turn lateral and anterior horn cells are overly stimulated to display various motor

9. Threadgill, F. D.: Afferent Conduction via the Sympathetic Ganglia Innervating the Extremities, Surgery **21**:575, 1947.

10. Moore, R. M., and Moore, R. E.: Studies on Pain-Sensibility of Arteries: I. Some Observations on the Pain-Sensibility of Arteries, Am. J. Physiol. **104**:259, 1933. Moore, R. M., and Singleton, A. O.: Studies on the Pain-Sensibility of Arteries: II. Peripheral Paths of Afferent Neurones from the Arteries of the Extremities and the Abdominal Aorta, Am. J. Physiol. **104**:267, 1933.

responses in the periphery. He laid stress on the activity of the internuncial pool and stated the belief that repeated interruption of the vicious circle of impulses either at the source or in the efferent portion of the circle may be curative. This concept of pain is attractive. It is known that the pain in causalgia and sympathetic dystrophy is usually the first and most prominent manifestation of the disorder, and it is not unreasonable to state that this is a result of sustained stimulation of sensory somatic fibers. It is difficult to understand why a temporary or permanent interruption of the efferent portion of the circle should bring about relief of pain. After the thirty to sixty minute period of procaine anesthetization is over, the same state of stimulation and impulse transmission exists as before the injection was given. Removal of the source of afferent stimulation by excision or procaine injection at the site of injury supports Livingston's concept of this type of pain.

SYMPATHETIC EFFERENT IMPULSES INCREASING SOMATIC SENSORY IMPULSES BY FIBER INTERACTION

In 1944, Doupe, Cullen and Chance [7] presented a theoretic explanation of causalgic pain based primarily on the experimental observations of Katz and Schmitt.[11] The latter authors had demonstrated that electrical stimulation of isolated nerve fibers augmented the excitability of adjacent nerve fibers. In June of 1944, Granit, Leksell and Skoglund [12] demonstrated by means of cathode ray oscillographic studies that an artificial synapse may be produced in a mixed peripheral nerve as a result of trauma and that facilitation of afferent impulses may result from efferent impulses. Doupe, Cullen and Chance [7] postulated that as a result of an artificial synapse in a partially damaged peripheral nerve, efferent sympathetic impulses produced painful afferent somatic impulses. They supported their theory by observations on several patients. Emotional stress and thermoregulatory demands invariably increased the patients' discomfort, presumably by means of increased sympathetic efferent activity. They also confirmed the observation of Tinel [13] that, in some instances, procaine anesthesia of the nerve distal to the site of injury produced dramatic relief. On the basis of these observations, Doupe, Cullen and Chance divided their patients into those with a proximal or distal causalgic syndrome, according to

11. Katz, B., and Schmitt, O. H.: A Note on Interaction between Nerve Fibers, J. Physiol. **100**:369, 1942.

12. Granit, R.; Leksell, L., and Skoglund, C. R.: Fibre Interaction in Injured or Compressed Region of Nerve, Brain **67**:125, 1944.

13. Tinel, M. J.: Causalgie du nerf médian, par blessure à la partie moyenne du bras; insufficance de la sympathectomie périartérielle; guérison par la section du nerf au poignet, Rev. neurol. **33**:79, 1918.

whether fiber interaction took place at the site of injury or at the nerve endings.

Since 1864, when Mitchell, Morehouse and Keen first described this syndrome, there have been insurmountable objections to every theory propounded for the explanation of this peculiar painful state. It is with avidity that one seizes on any new and reasonable explanation proffered. The ideas that Doupe, Cullen and Chance have proposed are exceedingly attractive, but there are some questions that I believe may be raised legitimately and, I trust, profitably. Doupe, Cullen and Chance have divided post-traumatic painful states into psychogenic, causalgic and dystrophic classes. They tend to minimize the dystrophic type of pain and ascribe it to nutritional factors and individual predispositions to mild circulatory disorders. They failed to mention that the majority of these patients with dystrophic pain respond to sympathetic interruption as satisfactorily as do those with causalgic pain. Many of these patients have pain as a result of a sprained ankle, a sprained finger or iliofemoral thrombophlebitis. There is no clinically demonstrable mixed nerve lesion.

The pain of sympathetic dystrophy is rarely confined to the peripheral distribution of a sensory nerve. Patients have been observed when an injury to the index finger led to a diffuse pain involving the whole hand and forearm. It is difficult to imagine fiber interaction at the site of trauma producing such pain. Doupe, Cullen and Chance divide their patients into those with distal or proximal causalgia on the basis of relief of pain by procaine injections proximal or distal to the site of injury. They postulate in the latter group that fiber interaction occurs at the nerve endings. There are no experimental or clinical observations to support such a view.

CLINICAL MANIFESTATIONS

Patients with sympathetic dystrophy are difficult to treat for many reasons. By the time they are seen by a neurovascular surgeon, months have ordinarily elapsed since the original injury or the disease started. They are discouraged and apprehensive. It is a rare patient who has not received a diagnosis of psychoneurosis or malingering. Many have claims pending before state industrial commissions and have been led to believe that their claims are untenable. In some of these patients, emotional disturbances have occurred with such severity and for so long a time that psychiatric therapy is necessary before and after treatment of their sympathetic dystrophy. There is sufficient evidence at the present time to maintain that the emotional instability is for the most part a result of the months of pain and discouragement these patients endure and not the cause of the changes observed in the extremity.

TABLE 1.—*Summary of*

Case Admission Date	Sex, Age	Original Trauma or Disease, Date	Type of Pain, Duration	Edema *	Hyperhidrosis *	Skin Temperature Difference (C.)
1 2/10/47	F 26	Sprained right ankle, June 1946	Severe aching, burning, 2 mo.	+	....	.....
2 4/15/47	F 25	Sprained left index finger, Sept. 1946	Severe throbbing, 7 mo.	+	++	—2.4
3 5/29/46	F 23	Acute deep venous thrombosis, postpartum left leg, Feb. 1946	Moderate burning, paresthesia, 3 mo.	+++	....	+4.5
4 8/25/46	M 33	Fracture great toe, left, 1922	Moderate aching, numbness, 25 yr.	....	....	—2.2
5 12/26/46	M 41	Thrombosis popliteal vein, left, Dec. 26, 1946	Severe aching, 30 hr.	....	....	—3.8
6 3/ 9/47	F 29	Thrombophlebitis thigh, superficial, right, Jan. 1947	Moderate aching, 7 wk.	....	....	.....
7 6/ 6/46	M 26	Sprained right wrist, March 1945	Moderate aching, 15 mo.	....	+	—1.6
8 5/25/47	M 46	Crushing injury of foot, right, June 1946	Moderate aching, 11 mo.	++	....	—1.0
9 5/31/46	M 43	Venous thrombosis, deep and superficial, both legs, 1943	Moderate aching, 3 yr.	+++	....	.....
10 9/24/46	M 53	Fracture surgical neck, humerus, right, July 1946	Severe aching, 8 wk.	+++	....	.....
11 9/14/46	M 27	Deep venous thrombosis, left leg, Aug. 1940	Moderate aching, 1 yr.	+	+	—1.3
12 5/13/46	M 45	Compound fracture tibia, left, 1944	Moderate aching, 18 mo.	+++	++	+3.2
13 12/16/46	F 52	Fracture metatarsal, right, second, Sept. 1946	Severe throbbing, 3 wk.	+	....	+2.0
14 8/ 1/46	M 69	Dislocation shoulder, right, repeated	Moderate burning, 1½ yr.	....	....	+1.2
15 1/ 9/47	F 45	Dislocation elbow, left, Volkmann's contracture, April 1946	Severe aching, 7 mo.	....	++	—2.0
16 5/16/46	F 37	Thrombophlebitis saphenous, traumatic, left, Dec. 1945	Moderate burning, 5 mo.	....	++	—1.0
17 5/28/47	F 55	Sprained ankle, right, March 15, 1947	Severe throbbing, aching, 6 wk.	++	....	+1.0
18 3/ 2/47	F 31	Sprained wrist, left, March 1946	Moderate aching, 1 yr.	....	++	—2.6
19 11/12/46	M 28	Torsion of neck, Oct. 1945	Moderate aching, left arm, 1 yr.	....	....	.....
20 12/ 3/46	M 41	Compound fractures, both tibias, April 1946	Severe aching, paresthesia, 7 mo.	....	++	.....
21 1/14/47	F 59	Cervical arthritis	Paresthesia, left, coldness, 6 mo.	++	....	—2.0
22 11/29/46	F 51	Fracture metacarpal hand, third left, Sept. 14, 1946	Severe throbbing, burning, 9 wk.	+++	++++	—4.0
23 6/16/47	M 42	Venous thrombosis, deep contusion, left leg, 1944	Moderate aching, burning, 3 yr.	++	....	.....
24 3/ 6/47	F 34	Compound fracture phalanx, second, left hand, Sept. 1946	Severe throbbing, burning, 6 mo.	+	++	—2.0
25 6/ 2/47	M 57	Compound fracture, tibia and fibula, right, Dec. 26, 1946	Moderate aching, 6 mo.	+	....	—2.0
26 7/16/47	M 25	Contusion thigh, left, 1943	Paresthesia, aching, 4 yr.	....	+	—1.5
27 8/17/47	F 45	Contusion thigh, left, Feb. 1945	Coldness, aching, 16 mo.	+	+	—1.8
28 8/19/47	F 48	Thrombophlebitis forearm, left, April 1947	Numbness, aching, 4 mo.	....	....	—2.0
29 10/17/44	M 47	Compound fracture, third right metacarpal, July 13, 1944	Throbbing, 2 mo.	+	++	—2.4
30 11/19/47	F 47	Colles fracture, right, Sept. 8, 1947	Throbbing, burning 6 wk.	....	....	—2.8
31 11/ 5/47	F 65	Fracture humerus, left, June 1947	Aching, 6 wk.	+	....	.....
32 11/11/47	F 29	Sprained right ankle, June 1947	Aching, burning, 4½ mo.	+	....	+3.6

* The symbols for 1, 2, 3 and 4 plus indicate the degree of the condition, from mild to severe.

Data in 32 Cases

Oscillometric Index			Diagnostic Studies					
Right	Left	Osteoporosis	Tetraethyl Ammonium Chloride, Mg. Intravenously	Procaine Block	Relief of Pain	Treatment, Date	Result	Complications
...	...	None	200	.....	24 hr.	Sympathectomy, lumbar, right, Feb. 15, 1947	Good	None
...	...	None	...	Stellate	6 hr.	Sympathectomy, thoracic, left, April 1916	Good	None
1.3	1.3	Spotty	...	Lumbar	24 hr.	Paravertebral block, June 24, 1946	Good	Contracture, corrected
1.7	0.8	None	...	Lumbar	24 hr.	Sympathectomy, lumbar, left, Aug. 1928	Good	None
0.6	0.1	None	200	→			Good	None
...	...	None	200	.....	None	Paravertebral blocks, March 11, 12 and 14, 1947	Good	None
...	...	.....	...	Thoracic	10 hr.	Sympathectomy, thoracic recommended	.....	.....
0.8	0.8	None	200	.....	8 hr.	Sympathectomy, lumbar recommended	.....	.....
1.6	1.6	None	...	Lumbar	3 hr.	Sympathectomies, lumbar June 17 and July 1, 1946	Good	Ulceration, supramalleolar
...	...	Patchy	...	Stellate	3 hr.	Stellate blocks (3), Sept. 26,27 and 28, 1946	Improved, sympathetic reaction	No return
...	...	None	...	Lumbar × 2	10 hr.	Sympathectomy, lumbar, left, Sept. 24, 1946	Good	None
0.8	0.8	Severe	Spinal anesthesia pontocaine		24 hr.	Sympathectomy, lumbar, left, May 14, 1946	Good	None
...	...	Slight	150	.....	Partial 45 min.	Paravertebral block Dec. 18, 1946	Good	None
...	...	.....	...	Thoracic	→	Aug. 2, 1946	Good	Vascular collapse rev.
...	...	Severe	250	.....	Hand (not finger)	Stellate block and sympathectomy recommended	.....	Morphine addiction
0.8	1.4	.....	...	Lumbar	24 hr.	Sympathectomy recommended	.....	.....
0.6	.47	Pronounced, patchy	200 (3)	.....	2 wk.	Sympathectomy recommended	.....	.....
...	...	None	...	Stellate	3 hr.	Sympathectomy, thoracic, left, March 7, 1947	Good	Aching neck, left
...	...	None	...	Stellate (3)	1-5 days	Sympathectomy, thoracic left, Dec. 13, 1946	Good	None
...	...	Pronounced, bilateral	...	Posterior tibial left	2 hr.	Sympathectomy, lumbar, bilateral, Dec. 4, 1910	Good	None
...	...	None	100	Stellate	2-3 hr.	Sympathectomy, thoracic, left, Jan. 16, 1947	Good	Paresthesia, mild
...	...	Pronounced	200 Twice a day (10)	Stellate	2-4 hr.	Sympathectomy, thoracic, left, Dec. 11, 1946	Good	Pain in shoulder, relieved
0.75	0.5	None	200-250 (2)	Lumbar	6-10 hr.	Sympathectomy, lumbar, left, July 7, 1947	Good	None
...	...	Pronounced	200 (3)	.....	3 wk.	Sympathectomies, left thoracic, left brachial, March 8, 1947	Good	Amputation of finger
0.37	0.5	Pronounced	250 (2)	Lumbar	3 hr.	Sympathectomy, lumbar, right, June 9, 1947	Good	Atelectasis
1.2	1.2	Mild	250	.....	10 min.	Sympathectomy, left lumbar, July 18, 1947	Good	Recurrence
				Splanchnic	24 hr.	Splanchnicectomy, low thoracic sympathectomy, Sept. 16, 1947	Good	None
1.3	1.3	Moderate	200	.....	4 hr.	Sympathectomy, lumbar, left, Aug. 18, 1947	Good	None
1.0	0.6	Mild	200	Stellate	12-24 hr.	Sympathectomy not recommended because of psychogenic factors		
...	...	Moderate	...	Thoracic	12 hr.	Right brachial periarterial sympathectomy, Oct. 24, 1944	90% relief	None
0.8	1.5	Moderate	...	Stellate (3)	→		Good	None
2.5	2.5	Moderate	...	Stellate	→		Good	None
1.8	1.0	Mild	200 (4)	→			80% relief	None

PREVIOUS DISEASE OR INJURY

Of the 32 patients seen at University Hospitals during the past three years, 6 had sprains of the wrist, finger or ankle; 1 had a torsion of the neck; 11 had suffered from fractures; 3 from contusions; 1 from cervical arthritis; 8 from venous thrombosis, and 2 from dislocations. The duration of the pain before treatment was instituted was from three weeks to twenty-five years. Most patients, however, were seen between the third and the eighth month after the onset of pain.

The type of pain complained of was of an aching, burning or throbbing character. Some patients complained of coldness and numbness. When paresthesias were complained of, it was noted that they did not correspond to the sensory distribution of either a peripheral nerve or root. The majority of patients complained of more than one type of pain. The pain was constant in all instances, although subject to variations in intensity during the day or night. All patients were either partially or completely disabled because of the pain. The intensity of the pain varied from no more than an annoying ache to unbearable throbbing and burning. Many of the patients with sympathetic dystrophy of a lower extremity when first seen were confined to bed or a wheel chair, and others were ambulatory only with the aid of crutches.

In 19 of the 32 patients edema was present. It was always confined to the hand or foot, and subsided promptly with bed rest and elevation of the extremity. In 13 patients hyperhidrosis was present. This was arbitrarily classified as 1 to 4 plus, based on a comparison with the normal extremity. As anticipated, the patients with an increased skin temperature in the affected extremity never displayed increased sudomotor activity, and that patient (22) who had the greatest reduction in skin temperature displayed the greatest amount of sudomotor activity.

Thirty of the patients had dermathermic readings recorded. Eighteen had a reduction in the skin temperature of the affected limb when compared with the normal side; 6 had an increased temperature, and in 6 the temperature was the same. The oscillometric index used in these studies was that described by Atlas.[14] Patients 3, 8, 9, 26, 27 and 31 had the same index for both extremities, although the skin temperature was elevated in patient 3, and reduced in patients 8, 26 and 27. In patients 4, 5, 23, 25, 28 and 30 the oscillometric index was reduced, and in 5 of these patients skin temperature was reduced. In patients 12, 16, 17 and 32 the index was increased, and in 3 of these patients the temperature of the skin was also increased. The results of these recordings show that there is a correlation between the oscillometric index and the skin temperature. They further suggest that

14. Atlas, L. N.: Oscillometry, Arch. Int. Med. **63**:1158, 1939.

there is little relation between the patient's pain and alterations in peripheral blood flow (table 2).

Seventeen of the patients showed osteoporosis of varying degrees, usually of spotty distribution (table 3). Twelve patients showed no osseous abnormalities. De Takats [5b] noted the fact that osteoporosis is not as characteristic of this syndrome as many authors have suggested. My observations tend to bear out this statement. The absence of osteoporosis should not deter the physician from instituting diagnostic studies and certainly should not in itself suggest a functional disorder.

Diagnostic studies consisted of the intravenous administration of tetraethyl ammonium chloride ("etamon chloride," supplied by Parke, Davis & Co.) and/or procaine injections into the regional sympa-

TABLE 2.—*Observations on Blood Flow*

Observation	No. of Patients
Increased blood flow	7
Decreased blood flow	18
Normal blood flow	6
Not determined	1
Total	32

TABLE 3.—*Data on Osteoporosis*

Observation	No. of Patients
Roentgenographic observation for osteoporosis	29
Osteoporosis present	17
Osteoporosis absent	12
Total	32

thetic ganglions. One patient received a spinal anesthetic, and 1, because of apprehension, was subjected to a peripheral nerve block. The patient who received the spinal anesthetic (12) experienced along with somatic anesthesia a satisfactory efferent sympathetic paralysis with a 6 C. (10.8 F.) rise in temperature and relief of pain in the dystrophic extremity for twenty-four hours. As a rule, however, paravertebral block is more satisfactory and convincing. The relief of pain following only efferent sympathetic paralysis gives the surgeon more information concerning the diagnosis and the ultimate effect of operative interruption of sympathetic pathways.

All patients who received either tetraethyl ammonium chloride or paravertebral procaine injections obtained immediate relief of pain. Three patients who claimed to be only partially relieved of their pain after the intravenous administration of 150 to 250 mg. of tetraethyl ammonium chloride subsequently were completely relieved by paravertebral procaine injections.

TREATMENT

There can be little question that many patients with mild posttraumatic neurovascular disorders recover spontaneously or with the aid of physical therapy. It is a rare patient, however, who is seen by a neurovascular surgeon before his pain has become so fixed that physical therapy efforts ordinarily accentuate his complaints. In the series of patients under discussion, it was thought necessary to perform sympathectomies twenty-one times on 17 patients. Two patients had bilateral operations, and 2 patients had two procedures. Six patients refused operative intervention. Eight patients obtained relief from the use of tetraethyl ammonium chloride or paravertebral procaine injections (table 4). In general, the results of temporary or permanent interruption of the regional sympathetic fibers were gratifying. All of the 25 patients who submitted to recommended therapy obtained relief of pain and were restored to social and economic usefulness. Two patients who did not receive benefit from the initial sympathectomy

TABLE 4.—*Treatment Data*

	No. of Patients
Number accepting therapy	25
Number relieved permanently by procaine sympathetic blocks or tetraethyl ammonium chloride	8
Number requiring sympathectomy	17
Total	32

will be discussed in detail, as each presents a different problem. Because of psychogenic factors, it was thought inadvisable to offer sympathectomy to 1 patient.

REPORT OF CASES

CASE 1 (26 in table 1).—A 25 year old man suffered a severe contusion of the left thigh in April 1943. After becoming ambulatory, he experienced severe aching in the thigh radiating down the leg diffusely. He was seen four years later at the University Hospitals. Examination revealed slight hyperhidrosis of the lower leg, a decreased skin temperature, a slightly cyanotic tinge to the skin when the extremity was dependent and a venous filling time of 14 seconds compared with 6 seconds in the right foot. Radiographic examination showed minimal but definite osteoporosis in the left foot. Administration of 250 mg. of tetraethyl ammonium chloride intravenously gave him complete relief of pain for ten minutes. On July 18, 1947, a left lumbar sympathectomy, consisting of excision of the first, second and third lumbar ganglions, was performed. For three weeks relief of pain was complete; then he gradually experienced a return of his former pain. He was readmitted to the hospital for study on September 14. Three hundred milligrams of tetraethyl ammonium chloride injected intravenously relieved the pain for thirty minutes. A spinal anesthetic which eliminated sensory perception up to a level of the twelfth thoracic segment, but which did not interrupt the sympathetic supply to the unaffected extremity, relieved the

pain for fifty minutes. This affirmed a conviction that the painful impulses were transmitted centripetally by way of somatic nerves. A splanchnic procaine block was performed with complete relief of pain for eight hours. On September 16 a splanchnicectomy and sympathectomy consisting of excision of the ninth, tenth, eleventh and twelfth thoracic ganglions were performed. In order to determine definitely whether the first lumbar ganglion had been excised at the time of the lumbar sympathectomy, the diaphragm was removed from the vertebral column. No remnants of the lumbar chain could be found. Complete relief of pain had persisted for four months at the time of last examination.

CASE 2 (24 in table 1).—A 34 year old woman suffered a compound fracture of the middle phalanx of the second finger, left hand, in September 1946. After the period of immobilization, severe burning and throbbing developed which spread to the other fingers, her hand and forearm. When first seen in March 1947, she would allow no one to touch the hand and all fingers were fixed in moderate flexion. There was no involvement of the thumb. Mild edema and moderate hyperhidrosis were present. Skin temperature of the involved hand was 2 C. (3.6 F.) less than the opposite side. Pronounced osteoporosis was present. Daily intravenous injections of 200 mg. of tetraethyl ammonium chloride for three days afforded complete relief for three weeks. The whole syndrome recurred with its original intensity, and a resection of the second thoracic sympathetic ganglion was performed through a supraclavicular approach. Complete relief of pain and restoration of mobility of all fingers except the second resulted from the operation. No sudomotor activity or epinephrine sensitivity could be demonstrated. A throbbing pain of moderate intensity, however, persisted in the second finger, and this gradually spread to the hand. Procaine injections of the digital nerves at the base of the second finger relieved the pain for thirty to sixty minutes. The possibility of a neuroma of one digital nerve at the site of the original injury was considered, but exploration failed to disclose any. Pain in the second finger persisted and procaine injections around the brachial artery were attempted. These successfully relieved the pain without producing sensory anesthesia. Although there was no demonstrable sudomotor activity in the extremity and there was every reason to believe that the hand had been completely sympathectomized. on the basis of the peribrachial procaine injections, a periarterial sympathectomy of the brachial artery was performed. This resulted in relief of the spontaneous pain. Because of the decided tenderness at the site of the injury and fixation of the proximal interphalangeal joint, an amputation of the finger was performed. This patient returned to work and at the time of last observation was completely free of pain.

COMMENT

These 2 patients represent only a few of the many difficulties encountered in treating patients with sympathetic dystrophy. The emotional instability seen in most of these patients is not to be ignored. This is especially true of the women who have suffered pain for weeks or months. It is true that some of them will have an entirely different personality after the operative relief of their pain. They lose their apprehension, indecision and antagonism and become almost over night pleasant persons. On the other hand, many of the patients will complain of pain in their incision out of proportion to objective obser-

vations. They tend to ascribe vague symptoms elsewhere to the operation, and it requires a considerable amount of patience and reassurance to return these patients to a healthy state. There have been a few patients who presented adequate evidence of organic disease for whom operative intervention or even repeated procaine injections could not be recommended. Patient 28 experienced superficial thrombophlebitis of the left forearm following a cholecystectomy and for four months thereafter complained of numbness and aching in three fingers and the palm of her hand. A reduced skin temperature and oscillometric index were present, and osteoporosis of the carpus and phalanges was observed radiographically. Relief of pain was obtained for twelve hours after a stellate block. The patient, however, believed that her symptoms were the result of poor hospital care. Three physicians who were attending the patient agreed that any further hospital therapy, no matter how successful, would be of little use in permanently satisfying the patient.

SUMMARY AND CONCLUSIONS

Many of the theories proposed to explain the pain of sympathetic dystrophy are discussed. Each presents concepts that are not wholly compatible with what has been observed clinically and experimentally. There is adequate basis in fact for believing that the total blood flow in an extremity is not primarily concerned with the pain. There is further reason to believe that the total increase in blood flow following sympathetic interruption is not in itself the means whereby relief of pain is obtained. The overwhelming amount of clinical evidence supports the view that removal of sympathetic impulses to the extremity relieves the pain. Whether such interruption is effective because of altering blood flow to sensitized areas of peripheral nerves or by means of reducing fiber interaction is not known. The cause of this disorder, however, is in the periphery. With the use of radioactive elements, localized disturbances of blood flow may be determined, and it is to be hoped that further elucidation of this problem will be presented in the near future.

TESTOSTERONE PROPIONATE IN TREATMENT OF RECURRENT CANCER OF THE BREAST

ARTHUR B. McGRAW, M.D.
DETROIT

DURING the sixteen months from October 1946 through January 1948, 12 women under care at the Henry Ford Hospital for breast cancer, recurrent after radical operation, were given testosterone propionate [1] and the resulting effects closely watched. Individual doses were mostly 150 mg. Aggregate total doses were from 450 to 6,225 mg. Injections were intramuscular in alternate buttocks. Given slowly, they have not produced pain, soreness or any late untoward local reactions. Only in the first 2 patients treated were there objectionable general reactions to the drug, and those were the result of unnecessary abruptness with large initial doses. There have been slight masculinizing effects in 3 patients, principally of the voice, none sufficient to create a problem. Of the 12 patients treated, 6 have died, but only 1 of the entire group failed to show some observable beneficial clinical response. In 6 of the 12, clinical improvement was striking, in 2 good and in 3 fair. Such observations have led my colleagues and me to add this small series to other reports that have appeared in the literature.[2]

Read at the Central Surgical Association, Chicago, Feb. 21, 1948.

1. The Schering Corporation furnished enough testosterone propionate in oil for investigative purposes for treatment of 10 of the 12 patients mentioned herein.

2. Loeser, A. A.: Hormone Therapy in Mastitis and Breast Cancer, Brit. M. J. **2**:319, 1938. Ulrich, P.: Testostérone (hormone mâle) et son rôle possible dans le traitement de certains cancers du sein, Acta, Union internat. contre cancer **4**:377-380, 1939. Farrow, J. H.: Effect of Sex Hormones on Skeletal Metastases from Breast Cancer, Surgery **16**:141-151, 1944. Fels, E.: Treatment of Breast Cancer with Testosterone Propionate, J. Clin. Endocrinol. **4**:121-125, 1944. Prudente, A.: Postoperative Prophylaxis of Recurrent Mammary Cancer with Testosterone Propionate, Surg., Gynec. & Obst. **80**:575-592, 1945. Adair, F. E., and Herrmann, J. B.: The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast, Ann. Surg. **123**:1023-1035, 1946. Nathanson, I. T.: Effect of Stilbestrol on Advanced Cancer of the Breast, Cancer Research **6**:484, 1946. Adair, F. E.: The Use of the Male Sex Hormone in Women with Breast Cancer, Surg., Gynec. & Obst. **84**:719-722, 1947. Schwander, H., and Marvin, H. N.: Treatment of Carcinoma of the Human Breast with Testosterone Propionate, J. Clin. Endocrinol. **7**:423-432, 1947. Chase, H. C.: Breast Cancer, Surg., Gynec. & Obst. **85**:712-720, 1947. Estrogens and Androgens in Mammary Cancer, report of the Council on Pharmacy and Chemistry, J. A. M. A. **135**:987-989 (Dec. 13) 1947. Adair, F. E.: Testosterone in the Treatment of Breast Carcinoma, M. Clin. North America **32**:18-36, 1948.

The effect of the drug we have observed most consistently has been the development, even in partly incapacitated patients, of an increased sense of physical well-being and of increased ability to carry on ordinary activities. When there is added to this subjective feeling of improvement a retardation of metastases, as has occurred in 7 patients, and occasionally an observable reversal of the destructive changes in bone metastases, as has occurred in 2, both patient and physician have reason to be encouraged.

Brief case histories of 2 patients will serve to illustrate the clinical observations just described.

REPORT OF CASES

CASE 1.—In November 1939, F. C., a 67 year old housewife, consulted us regarding a subcutaneous nodule that had appeared beneath a scar on her right anterior thoracic wall. Seven years earlier she had had both breasts removed elsewhere, allegedly for chronic cystic mastitis. Since biopsy of this nodule revealed medullary carcinoma with scirrhous areas, a radical right axillary and pectoral muscle dissection was immediately performed. The axillary lymph nodes were not demonstrably invaded by tumor. No preoperative roentgen therapy was given, or any immediately after operation. Five and one-half years later, in June 1945, a small solitary metastasis appeared on the contralateral anterior thoracic wall, and was treated by excision and sharply localized irradiation. Another year passed before several other subcutaneous nodules appeared. At that time back pain also developed and was accounted for by early osteoblastic changes observed by roentgenogram in several dorsal vertebrae. Roentgen therapy was given to the left side of the thoracic wall and upper part of the spine. The cutaneous nodules regressed slightly, but the back pain was not relieved. In the early autumn of 1946, the use of testosterone was begun. The initial dose was large (150 mg. intramuscularly), and for four days the patient experienced decided malaise, nausea and a little fever. She wished to continue treatment, however, and treatment with the same dose of 150 mg. was continued at intervals of three to five days for 12 doses. After the second dose the malaise began to subside, and after the fourth dose there began to develop a sense of generalized improvement. Back pain, which roentgen therapy had not wholly relieved, ceased, and she regained 5 pounds (2 Kg.) of the weight she had lost. From October 1946 through August 1947, this patient received 4,750 mg. of testosterone in three courses of three months each, with one month of freedom from treatment intervening between courses. In each course after the first the initial dose was reduced to 50 mg., increased by 25 mg. per injection to a maximum of 150 mg. As of the time of reporting, the appearance of the lesions of the spine in roentgenograms had remained static and no further roentgen therapy had been given the spine. A few sharply localized roentgen treatments were applied to isolated new cutaneous metastases, most of the previously existing lesions having temporarily ceased to grow. In the autumn of 1947, however, a widespread reactivation of subcutaneous metastases occurred. Since our research supply of testosterone had been exhausted and since the patient was unable to afford the retail cost of the drug, treatment with testosterone was stopped. Bearing in mind the observations from the use of diethylstilbestrol reported by Nathanson, we began administra-

tion of that drug and built it up gradually to 20 milligrams per day. At the end of two months intolerance to diethylstilbestrol developed, but during that brief period it was our impression that arrest and slight regression of the reactivated cutaneous nodules occurred. At the time of reporting, the patient was still living and had been ambulatory and active during the sixteen months since she first received testosterone. One cutaneous nodule had undergone indolent ulceration.

CASE 2.—In November 1944, M. D., a widow of 53 years of age, underwent a left radical mastectomy for a medullary carcinoma. No involved axillary nodes were demonstrated at operation. The area of operation was irradiated through three ports as soon as the wound had healed. Sixteen months later, in March 1946, she began to have pain in the lower part of the back and left hip. Roentgenograms taken at that time showed small but suspicious intertrochanteric areas of radiolucency in the left femur. Although progress roentgenograms in December of the same year showed no bone destruction, the patient's pain had continued, and she was therefore given several empiric roentgen treatments over the left iliolumbar area. Moderate remissions and frequent exacerbations of pain continued into 1947 and further bilateral lumbar irradiation was given in March of that year, again without benefit. By the end of May 1947, the patient was so uncomfortable that she was admitted to the hospital for bed rest and a trial of testosterone in 150 mg. doses every other day. Her pain began to lessen and then ceased. A feeling of well-being began to develop, but shortly after admission an impacted pathologic fracture of the neck of the left femur was detected by roentgenogram, with osteolytic changes surrounding the fracture site. A plaster hip spica was applied, and the large doses of testosterone were continued to a total of 6,225 mg. At the end of three months callus was evident; at the end of four months union had occurred, and at the end of five months the patient left the hospital walking alone.

In striking contrast to the aforementioned 2 treated patients is the terminal course of the following patient who underwent radical mastectomy, who died in 1946, shortly before testosterone became available to us:

CASE 3.—In March 1939, I. B., a 52 year old spinster holding a responsible secretarial position, underwent radical mastectomy for a medullary carcinoma of the left breast without demonstrable axillary nodes. Nevertheless, she was given prophylactic postoperative roentgen therapy to the operated area immediately after the wound had healed. For six years she remained subjectively and clinically free from signs of recurrence or metastasis, but in March 1945 she noticed an enlarged left supraclavicular lymph node. Under localized roentgen therapy the node regressed, but eleven months later, in February 1946, pain commenced in the left upper part of the thorax and was shown by roentgenogram to be associated with osteolytic lesions of several ribs. Two months later similar osteolytic areas were demonstrated in various vertebrae and in the pelvis. Palliative roentgen therapy was ineffective. Because of pain from these bone lesions this patient was partially disabled and in continuous discomfort during February and March. During the next five months, until her death in August, she was not only bedridden but literally flat on her back and immobile on account of the severe pain associated with movement or with assumption of any other than the supine position.

EFFECTS ON BONE METASTASES IN OTHER PATIENTS

In 7 patients besides the patient described in case 2, the metastatic lesions were principally of bone. In 5, arrest of progress of bone metastases was noted following testosterone treatment. In 1 patient there has occurred slight recalcification of osteolytic lesions of the pelvis, femur and of a collapsed lumbar vertebra. This latter patient became ambulatory without discomfort in a supportive corset after initial complete incapacitation. In these patients alkaline phosphatase levels in the blood have been slightly augmented, but blood calcium and phosphorus levels have not been significantly affected. Roentgen therapy was given the involved bones of 3 of this group of patients, but only in doses calculated to allay pain.

EFFECTS OF CUTANEOUS METASTASES

Six patients in all showed cutaneous or subcutaneous metastases at the time their testosterone injections were begun. In 1 patient no change occurred in the cutaneous nodules. In 4 patients, including the patient in case 1, there occurred slight temporary retardation of growth. In 1 patient the retarding effect of testosterone appears to have been more pronounced and is of considerable interest. This 69 year old woman had a cutaneous nodule fixed to the thoracic wall in the operation area six years after she had undergone a radical mastectomy. While under testosterone treatment the nodule was widely excised and a split thickness graft applied to the defect, resting partly on normal tissues and partly on obviously exposed tumor tissue. The graft took in its entirety. Although lymph nodes bearing tumor subsequently appeared in the opposite axilla and were excised, there was for the space of fifteen months no growth of tumor through the graft or other cutaneous recurrence.

TERMINAL COURSE OF 6 PATIENTS

Of 6 patients who have died, 1 died six months after treatment with testosterone was started, without any observable improvement at any time. A second patient, who showed fairly sustained retardation of cutaneous recurrence and subjective improvement, died at home in coma from associated diabetes mellitus, ten months after receiving testosterone. Two other patients died in three months or less after treatment was started, but experienced definite subjective relief lasting into their terminal stages. Two patients died in the hospital of pleuropulmonary metastases. One of these women began to receive testosterone in late September 1947, after having become totally incapacitated from pleural effusion and backache from vertebral metastases. After receiving 500 mg. orally and an equal amount intramuscularly, she experienced so much subjective improvement that for six weeks she

resumed full duties as a school teacher. Her final hospital stay was only seventeen days and not marked by great discomfort until the last two days. The other patient, in spite of needing repeated thoracenteses, was not orthopneic until her final admission and carried out many of her household duties for four months, until two weeks before her death. Neither of these women required morphine at any time, and neither experienced nearly as much terminal distress as we have been accustomed to observe in similar patients. We consider this apparent ability to sustain some patients in comparative comfort until a mercifully rapid terminal episode supervenes one of the most valuable effects ascribable to the use of testosterone.

Summary of Data in Twelve Cases

Case No.	Age at Operation	Year of Operation	Interval Until Reactivation	Sites of Reactivation	Testosterone Therapy Begun	Total Dose (Mg.)	Effects		Present Status
							Function	Lesion	
1	59	Feb. 1941	56 mo. Oct. 1945	Lung, pleura, cervical nodes	Oct. 1946	450	Fair	Slight	Died 1/47; survived 3 mo.
2	38	June 1944	16 mo. Oct. 1945	Skin, lung, pleura, ribs, spine	Oct. 1946	1,500	Good	Slight	Died 2/47; survived 4 mo.
3	67	Nov. 1939	67 mo. June 1945	Skin, cervical nodes, ribs, spine	Oct. 1946	4,750	Very good	Good	Living, 15 mo.
4	60	Aug. 1940	50 mo. Oct. 1946	Skin, other axilla	Nov. 1946	1,350	Very good	Good	Living, 14 mo.
5	48	May 1944	14 mo. July 1945	Skin, lung	Nov. 1946	1,800	None	None	Died 6/47; survived 7 mo.
6	63	May 1945	18 mo. Nov. 1946	Skin	Nov. 1946	1,250	Fair	Good	Died 8/47; survived 8 mo.
7	52	June 1945	16 mo. Oct. 1946	Spine (multiple)	Jan. 1947	2,975	Very good	Good	Living, 12 mo.
8	56	Nov. 1944	16 mo. June 1946	Pelvis, femur	May 1947	6,225	Very good	Very good	Living, 9 mo.
9	61	Elswh. 1942	? 1947	Spine, pelvis	July 1947	1,350	Good	Fair	Living, 7 mo.
10	38	May 1947	3 mo. Aug. 1947	Spine, pelvis, liver	Aug. 1947	750	Fair	None	Died 10/47; survived 2 mo.
11	33	Aug. 1943	36 mo. Aug. 1946	Lung, pleura, spine, pericardium	Sept. 1947	2,000	Very good	Slight	Died 11/47; survived 2 mo.
12	51	June 1941	74 mo. Sept. 1947	Spine, pelvis, femur	Oct. 1947	3,000	Very good	Good	Living, 4 mo.

In the table are recorded those facts that seem significant regarding the 12 treated patients whose responses to testosterone have been discussed. The nature of their lesions are indicated, together with the period of treatment, amounts given and results noted.

CONCLUSIONS

In conclusion, the current opinions and practice of my colleagues and I regarding testosterone propionate in the treatment of breast carcinoma are as follows:

1. Testosterone propionate does not cure mammary cancer.

2. Its use as a palliative agent has a logical basis, and its observed beneficial effects when so used are such as to encourage further use and study.

3. Its use rather dependably induces subjective improvement, often in pronounced degree and sometimes of considerable duration.

4. Subjective improvement is sometimes accompanied with temporary retardation of bone and skin metastases and occasionally by their regression.

5. The patients in our series who have responded best have been those receiving both a large weekly dose (200 to 300 mg.) and a large aggregate dose (3,000 to 6,000 mg.).

6. If maximal individual doses are attained gradually, commencing with no more than 50 mg., neither undesirable local or general reactions occur.

7. Our best results with respect to duration of palliation have been in those patients whose metastases have been principally or solely in bone.

8. Used as a palliative agent, we consider testosterone propionate an adjunct to, not a substitute for, roentgen therapy.

ESOPHAGEAL VARICES

Two Cases with Different Surgical Approach

HERBERT H. DAVIS, M.D.
OMAHA

ESOPHAGEAL varices with repeated severe hemorrhages are due usually to varying degrees of portal vein obstruction. The increased portal vein pressure forces blood into the esophageal veins. The veins in the submucosa of the esophagus are poorly supported by loose connective tissue. Thus varicosities may develop. The sucking effect of respiration accentuates this.

There is evidence that Banti's syndrome of splenomegaly, anemia, leukopenia and esophageal varices, with hemorrhage and at times ascites, is due not to primary disease of the spleen but rather to varying degrees of obstruction in the portal system. Whipple [1] and his co-workers, by blocking the portal vein experimentally, were able to produce Banti's syndrome. The term "congestive splenomegaly" suggested by Larrabee in 1934 is more descriptive of this condition.

Portal hypertension may be due to intrahepatic or extrahepatic block. The former is usually the result of cirrhosis. Extrahepatic block may be due to fibrous stenosis or cavernomatous transformation of the portal vein.

At the present time there is no completely satisfactory treatment for esophageal varices, which frequently cause serious recurrent hemorrhages. However, in recent years there is increased interest in this problem. Medical management of cirrhosis of the liver is greatly improved. The best surgical treatment seems to be injection of sclerosing solution into the esophageal varices through the esophagoscope, portacaval shunt either by anastomosis of the portal vein to the inferior vena cava or of the splenic vein to the left renal vein, or transthoracic removal of the lower esophagus and possibly of part of the stomach.

Moersch [2] reported 22 patients treated by injection of the esophageal veins with a sclerosing agent. Three or more years later 12 had had no more bleeding, 4 were living with continued hemorrhages, 3 were dead of hemorrhages and 4 were dead of unknown or unrelated causes.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

Blakemore [3] reported 32 patients treated by portacaval shunt, with 5 deaths. In a previous report he gave the results in 19 patients. Of these, 8 had one or more episodes of hemorrhage. Two of these 8 died. Eleven were well.

Phemister and Humphreys [4] reported improvement in 1 patient treated by total gastrectomy and relief in another by transthoracic esophagogastric resection.

I wish to report 2 patients with repeated severe esophageal hemorrhages. Each had had splenectomy performed elsewhere, without relief of the hemorrhages. One was treated by ligation of the coronary vein and the other by anastomosis of the portal vein to the inferior vena cava.

REPORT OF CASES

CASE 1.—D. B., a boy age 15, was admitted April 8, 1946, to Methodist Hospital after a severe esophageal hemorrhage. As an infant he was pale and had a large abdomen. At the age of 10, after having had measles, he had a hemorrhage from the gastrointestinal tract. A splenectomy was done. After this he was well for four years. On two occasions in December 1945, he had hemorrhages from the gastrointestinal tract. On March 24, 1946, he had hematemesis again. The blood loss was massive, and he lost consciousness. He was given some medication by Dr. Guy Tucker for the purpose of aiding blood coagulation. The next morning he was given a blood transfusion. Later in the day, when he attempted to get out of bed, he had another severe hematemesis and lost consciousness. He was taken to a hospital in Hastings, Neb., where he remained unconscious the rest of that day and night. The following day he was given three blood transfusions. On April 8, fifteen days after the beginning of this severe episode, he entered Methodist Hospital in Omaha on the service of Dr. W. A. Cassidy, who, on esophagoscopic examination, noted that the upper portion of the esophagus showed a few small dilated veins, but was otherwise normal. The remainder of the esophagus presented a normal appearance until a level of about 5 cm. from the cardia was reached. At this point many large tortuous varicosities were encountered.

The boy was moderately pale and his pulse regular and of good quality. There was a soft systolic murmur at the apex of the heart. The systolic blood pressure was 126 and the diastolic 60 mm. of mercury. There was a healed scar in the left upper quadrant of the abdomen from his previous splenectomy. The liver was not palpable. There were no enlarged collateral veins in the thorax, abdomen or anus. Blood examination revealed 3,470,000 red blood cells, 7,100 white blood cells and a platelet count of 426,810.

Celiotomy was done April 11. The spleen had been removed. The liver was normal to inspection and palpation. There was no dilatation of the veins along the curvatures of the stomach or of the superior or inferior mesenteric veins. The portal vein was normal size. The splenic vein was 8 mm. in diameter. It was carefully dissected, and the coronary vein was found to be dilated and to enter the splenic vein about 5 cm. from its juncture with the portal vein. An

area of stenosis of the splenic vein was found proximal to the juncture of these two veins. There was no stenosis of the portal vein itself. The splenic vein was much smaller distally; therefore, it was not possible to do a splenorenal vein anastomosis. The coronary vein and another vein accompanying it were cut between ligatures. The gastrohepatic ligament was sutured, and the wound was closed.

The next day the highest pulse rate was 104, temperature 102 F., red blood cell count 3,670,000, hemoglobin 68 per cent, white blood cell count 24,700, with polymorphonuclear cells 74 per cent. During the next few days he was rather badly distended. During his convalescence he was given two blood transfusions. There was moderate consolidation at the base of the left lung a week after operation, which cleared up readily. He was dismissed in good condition fifteen days after the operation, having had no postoperative esophageal hemorrhage.

A letter from his parents dated May 27, a month after he left the hospital, stated that he had gained 13 pounds (6 Kg.) since returning home. He felt well and had a fine appetite. They asked whether he could begin working. He had had no further hemorrhages. Another letter, dated November 30, stated that he had gained from his previous weight of 90 pounds (41 Kg.) to 120 pounds (54 Kg.) in the seven months since his operation and that he had had no bleeding whatever. He had also grown much taller. Aside from not playing basketball and football, he had been doing all the activities of any normal boy. He was fine until Sept. 4, 1947, seventeen months after his operation, when he had another severe esophageal hemorrhage. Following two blood transfusions his red blood cell count was 4,230,000, with 76 per cent hemoglobin. Esophagoscopy by Dr. Cassidy on September 23 showed that the varicosities were noticeably less conspicious, but were still present in rather abundant quantity. It was decided to inject the remaining varicosities with sodium morrhuate. The first injection was on November 11, at which time 1 cc. of sodium morrhuate was injected. The procedure was repeated on December 10, when 2 cc. of sodium morrhuate was injected. The third and most recent injection of sodium morrhuate was on December 31, when 3 cc. of sodium morrhuate was used. At this time no further reduction in the size of the varicosities was observed. It was decided to continue these injections.

Case 2.—P. V., a man aged 31, was admitted to Clarkson Hospital on June 3, 1946, referred by Dr. A. B. Anderson of Pawnee City, Neb. Five years previously he had had two hemorrhages three months apart. He received transfusions each time. Then at the Mayo Clinic he was told that he had bled from esophageal varices, and a splenectomy was done. After this he was well until the spring of 1945, when he had another hemorrhage. He had felt tired since then.

Physical examination revealed a rather pale young man. There was a systolic murmur at the apex of the heart. His blood pressure was 120 systolic and 70 diastolic. There were scars of his previous splenectomy and of an appendectomy. There was no tenderness or masses in the abdomen; the liver was not palpable, and there were no hemorrhoids. The red blood cell count was 3,200,000, hemoglobin 8.6 Gm., white blood cell count 8,300 and platelets 374,000. Bleeding time was 2 minutes, coagulation time 3 minutes, and the reaction of the blood to the Massini test was negative.

Esophagoscopy by Dr. W. A. Cassidy showed slight dilatation of the esophagus throughout its entire length. The mucosa showed a mild superficial inflammatory process and the presence of some gray abnormal secretion. When the esophagoscope reached a level of 32 cm. from the upper teeth, large varices were observed. The dilated vessels were apparent from this point down to the cardia. Some of the vessels were extremely large and protruded into the lumen of the esophagus, resembling polypoid structures.

He was given a blood transfusion two days before operation. At operation the liver was found to be hard, nodular and possibly slightly smaller than normal—typical of Laennec's cirrhosis. The spleen had been removed previously. There was no ascites. The portal vein, which was approximately 12 mm. in diameter, was dissected out. The inferior vena cava, both above and below the renal veins, was exposed. The portal vein was ligated at its entrance into the liver and cut across just below this. The distal segment was anastomosed end to side with the inferior vena cava, with interrupted sutures. During this procedure, when the vena cava was clamped off above the renal veins, the systolic blood pressure dropped to 70 mm. of mercury, but immediately after the clamps were removed it rose to 120 mm. of mercury. The wound was closed.

His postoperative course was uneventful, his highest temperature being 100 F. and pulse rate 92.

He remained well until Aug. 13, 1946 (two months and seven days after operation), when he had another severe hemorrhage, requiring two blood transfusions. On Feb. 19, 1947, he had another massive hemorrhage, lasting thirty-six hours. Forty-eight hours after its cessation his hemoglobin was 9.8 Gm. He had other hemorrhages, on May 4 and December 4. After each of these his hemoglobin was below 12 Gm. In July his physician, Dr. Sanford Rathbun, reported his red blood cell count to be 4,200,000 and hemoglobin 14 Gm. The sulfbromophthalein sodium test showed no retention at 45 or 60 minutes, and the reaction to the cephalin flocculation test was negative. Except for the four hemorrhages in the twenty months following operation, he was well and able to work full time at the time of writing. He had no enlarged collateral veins, which could occur if thrombosis had developed at the site of anastomosis.

COMMENT

Both patients had had previous splenectomies with temporary improvement. However, the splenomegaly was the result of portal hypertension rather than the cause. Neither could have a splenorenal vein anastomosis because of the previous splenectomy. The first patient was treated by coronary vein ligation with considerable improvement, but still had some hemorrhages later. The second patient, with an Eck fistula operation, also was improved, but had four postoperative hemorrhages. Probably the pressure in the esophageal veins had been reduced in each case. The walls of the veins had been weakened and stretched out by the previous portal hypertension. Their diameter in places was probably two to three times normal size. As the area of a tube is increased, the pressure on the wall is greater. Therefore, the venous

pressure is greatest in the area of varicosities, which also have weak walls.

It seems as though the principles applied to the treatment of varicose veins of the legs may be applied to the treatment of esophageal varices. In the leg, saphenous vein ligation decreases the pressure in the varicosities, but the veins remain enlarged until obliterated by injections of sclerosing solutions. Applying this principle, it may be advisable to follow portacaval anastomosis by the injection of sclerosing solution into the esophageal varices through the esophagoscope.

SUMMARY AND CONCLUSION

Two patients with bleeding esophageal varices are reported, one treated by coronary vein ligation and the other by anastomosis of the portal vein to the inferior vena cava. The results in both procedures were far from perfect. It is suggested that, in the patients who bleed following these operations, the varices be injected with sclerosing solution through the esophagoscope.

REEVALUATION OF PENICILLIN DOSAGE SCHEDULES

W. A. ALTEMEIER, M.D.
CINCINNATI

THUS FAR, it has been assumed that successful penicillin therapy of susceptible surgical infections depended primarily on the maintenance of a therapeutic concentration of this agent in the blood and tissues. A concentration of 0.03 unit per cubic centimeter has usually been recognized as a therapeutic level. The origin of this concept was probably the result of a transfer of experimental and clinical experience with the sulfonamide drugs.

At the time of its introduction to clinical surgery, penicillin was given by continuous infusion, either intravenously or intramuscularly, in the majority of instances. Because of the patient's discomfort and the amount of time and effort needed to insure its efficiency, this method was soon abandoned in favor of single injections made at intervals of two to four hours. Although this plan did not maintain a constant level, it insured a concentration of penicillin in excess of the therapeutic dose in most instances. In this manner, the rapid excretion was offset by the administration of penicillin either continuously or at short intervals, and effective therapy was unquestionably obtained in susceptible surgical infections.[1]

The inconvenience of these methods both to the patient and the physician and the difficulty and almost impossibility of administering penicillin to any one but a hospitalized patient led to the development of other methods devised to overcome these objections and to extend the usefulness of penicillin to ambulatory or unhospitalized patients. The plans advanced have followed three lines of investigation: delayed absorption, delayed excretion and oral administration. Delayed absorption has been accomplished by the use of preparations of penicillin containing 300,000 units in oil and wax[2] or oil in pectin.[3] Both

---

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 21, 1948.

From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital, Cincinnati.

1. (*a*) Altemeier, W. A.: Penicillin in Surgery, South. M. J. **37**:494, 1944. (*b*) Altemeier, W. A., and Wadsworth, C. L.: Penicillin— Its Use in Surgery and Influence on Earlier Types of Chemotherapy, Surg., Gynec. & Obst. **84**:541, 1947.

2. Romanski, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, Am. J. Med. **1**:395, 1946.

3. Welch, H.; Hirsh, H. L.; Taggart, S. R., and Smith, G. M.: Penicillin in Oil and Pectin, read before the Study Section of General Session Seminar of the National Institute of Health, September 1947.

methods can be expected to maintain an effective blood level for twenty-four or more hours in 70 to 80 per cent of the cases, and, if the dose is increased to 400,000 units, a satisfactory level will usually be maintained for twenty-four hours in practically all of the cases. More recently, the administration of procaine penicillin G in oil has produced excellent results.[4] The pectin in oil and the procaine penicillin preparations apparently have certain advantages over the oil and wax preparations, including a reduced incidence of pain and local reactions. Experimental studies suggest that bismuth preparations, silver preparations and mercury salts of penicillin also may be used to prolong the blood levels.[5]

The most satisfactory method of decreasing the excretion of penicillin is the oral administration of caronamide in doses of 3 Gm. every four hours for periods of two to nineteen days.[6] This may be used to decrease the interval between injections of aqueous penicillin, to enhance the blood levels two to seven times or to decrease the amount of the antibiotic necessary for treatment. Two of its disadvantages are the large daily doses required and the nausea it produces in some instances.

The oral administration of buffered penicillin has been used effectively, and the recommended dose is five times that of the necessary parenteral dose. The ingestion of 100,000 units of buffered penicillin at intervals of four to six hours can usually be depended on to produce and maintain a satisfactory concentration in the blood. Although this method of administration should be limited in its scope of application, it can be used effectively in selected cases, particularly in ambulatory patients.

It is well established, therefore, that the administration of adequate amounts of penicillin by any dosage schedule which maintains a more or less constant concentration of the agent in the circulating blood will produce efficient chemotherapy. However, it is not established that the maintenance of this therapeutic level in the blood is necessary for successful treatment, and evidence is accumulating that penicillin's bacteriostatic effect persists after its disappearance from the blood.

---

4. Herrell, W. E.; Nichols. Z. R., and Heilman, F. R.: Procaine Penicillin G (Duracillin): A New Salt of Penicillin Which Prolongs the Action of Penicillin, Proc. Staff Meet., Mayo Clin. **22**:567, 1947.

5. Monash, S.: The Use of Bismuth, Silver, and Mercury Salts of Penicillin for Prolongation of Penicillin Blood Levels: Preliminary Report, J. Invest. Dermat. **9**:157, 1947; The Use of Insoluble Penicillin Salts for the Prolongation of Penicillin Blood Levels, Science **106**:370, 1947.

6. Loewe, L.; Eiber, H. B., and Alterwerber, E.: Enhancement of Penicillin Blood Levels Following Oral Administration of Caronamide, Science **106**:494, 1947.

The results of Tillett and his co-workers [7] in 1944 suggested that the antibacterial effects of penicillin on invasive pneumococci inhibited their growth for a considerable period after blood concentrations were no longer measurable. When injections were made at intervals of twelve to sixteen hours, their results in a small number of cases seemed to be just as satisfactory as those obtained with more frequent injections. Similar inhibitory effects on streptococci infecting mice for eight or more hours were suggested by the studies of Jawetz [8] in 1946. The investigations of Zubrod [9] in hemolytic streptococcic infections of mice also indicated that the interval between doses of an aqueous solution of penicillin could be greatly increased beyond four hours. More recently Marshall,[10] after discussing the discrepancies in the methods of chemotherapy and indicating his belief that the maintenance of a more or less constant blood concentration was unnecessary for efficient treatment in human beings, advocated carefully controlled clinical trials to evaluate the efficiency of three, two or even one injection per day in infections in human beings.

MATERIALS AND METHODS

The current acute shortage of nursing personnel has stimulated my co-workers and me to explore the clinical effectiveness of aqueous penicillin administered intramuscularly every eight to twelve hours. During the past five months, we have given treatment in 87 selected cases of established surgical infections at the Cincinnati General and neighboring hospitals. In the majority of instances, externally located infections of moderate degree and known causation were chosen for study. Most of the cases were of infections produced primarily by the hemolytic Staphylococcus aureus, but the series included 6 instances of hemolytic streptococcic, 5 of pneumococcic and 12 of mixed bacterial infections (table).

Each patient was treated with either 100,000 units of penicillin at intervals of eight hours or 150,000 units at intervals of twelve hours. The penicillin was dissolved in isotonic sodium chloride solution and injected intramuscularly, with a volume of 1 cc. per hundred thousand units. Determinations of blood levels were made every two hours in 46 of the patients to determine the concentration of penicillin produced by one intramuscular injection. Whenever possible, the infecting bacteria were identified at the start of penicillin therapy and their susceptibility to penicillin determined in vitro. Studies were also made to determine the degree and duration of any inhibitory effect on the growth of five strains of hemolytic S. aureus produced by their exposure for two hours in vitro to 2 units of penicillin per cubic centimeter.

---

7. Tillett, W. S.; Cambier, M. J., and McCormack, J. E.: Treatment of Lobar Pneumonia and Pneumococcal Empyema with Penicillin, Bull. New York Acad. Med. **20**:142, 1944.

8. Jawetz, E.: Dynamics of Action of Penicillin in Experimental Animals: Observations of Mice, Arch. Int. Med. **77**:1 (Jan.) 1946.

9. Zubrod, C. G.: Comparative Efficiency of Single and Multiple Dosage Regimens of the Penicillins, Bull. Johns Hopkins Hosp. **81**:400, 1947.

10. Marshall, E. K.: The Dosage Schedule of Penicillin, read before the Antibiotic Study Section, Seminar held at National Institute of Health, October 1947.

RESULTS

Penicillin Blood Levels.—Considerable variation was obtained in the blood levels produced by a single intramuscular injection of 100,000 units of penicillin. Concentrations in excess of 0.03 unit per cubic centimeter were maintained for at least three hours in 100 per cent

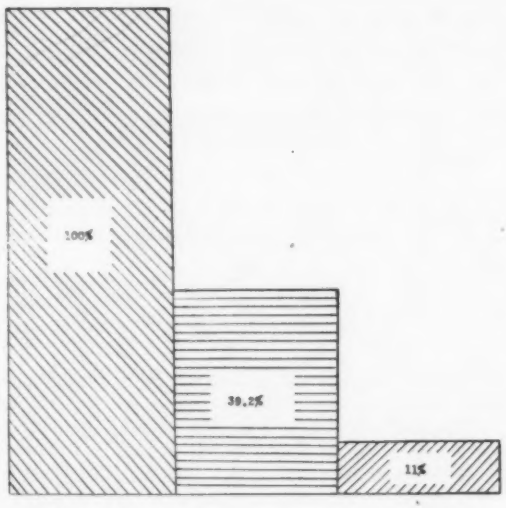


Fig. 1.—Duration of blood levels in excess of 0.03 unit per cubic centimeter produced by a single injection of 100,000 units of penicillin in aqueous solution in 46 cases. The highest level was maintained up to three hours, 39.2 per cent from three to five hours and 11 per cent from five to seven hours.

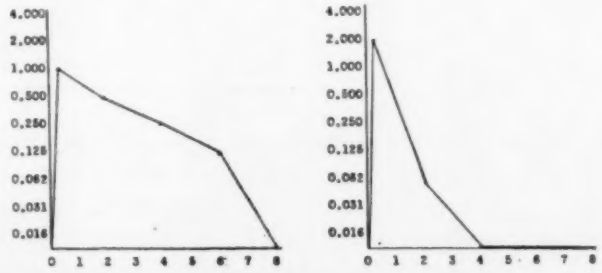


Fig. 2.—Variation in blood levels obtained following a single injection of 100,000 units of penicillin in aqueous solution given intramuscularly. The vertical columns of figures show the units of penicillin per cubic centimeter of serum, and the horizontal row of figures shows the time in hours.

of the cases, for three to five hours in 39.2 per cent of the cases and from five to seven hours in 11 per cent of the cases (fig. 1). The two extremes of variation encountered in blood levels are illustrated in figure 2.

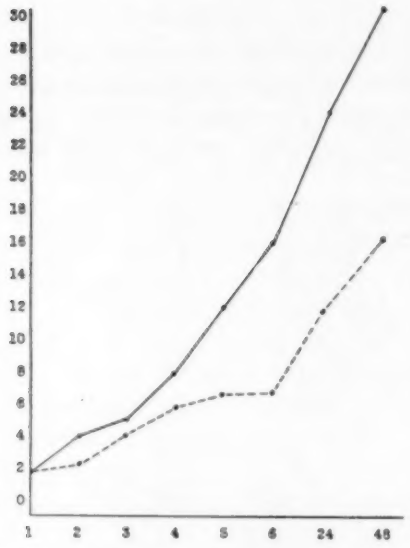


Fig. 3.—Illustration of the lag in growth of hemolytic Staphylococcus aureus (Rockhold strain) produced by two hours of exposure to 2 units of penicillin per cubic centimeter. The unbroken line indicates no exposure to penicillin, and the broken line indicates one hour of exposure to penicillin. The horizontal row of figures shows the time in hours.

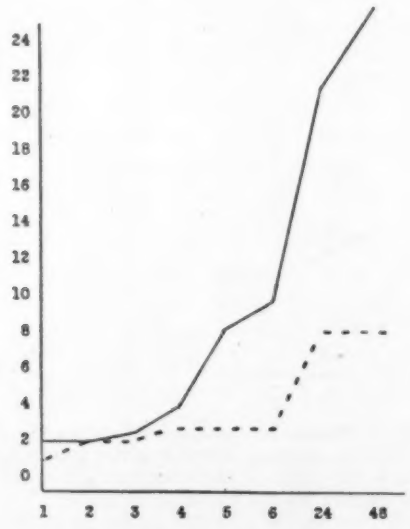


Fig. 4.—Illustration of the lag in growth of hemolytic Staphylococcus aureus (Tucker strain) produced by two hours of exposure to 2 units of penicillin per cubic centimeter. The unbroken line indicates no exposure to penicillin, and the broken line indicates one hour of exposure to penicillin. The vertical column of figures shows the units of turbidity, and the horizontal row of figures shows the time in hours.

Persistence of Inhibitory Effect on Bacterial Growth.—When five strains of the hemolytic S. aureus isolated from established infections in human beings were exposed for two hours to the effect of 2 units of penicillin per cubic centimeter of medium, a definite lag in their growth persisted for eight to twenty-four hours after the penicillin was removed and the organism reinoculated into fresh mediums. Figures 3 and 4 illustrate this inhibition through measurements of the turbidity produced by the growth of two strains of the hemolytic S. aureus with and without exposure to the antibiotic agent.

Clinical Results.—The clinical results obtained in this series of selected cases compared favorably with those anticipated with the three

Clinical Results with Eight Hour Penicillin Dosage Schedule

Diagnosis	Number of Cases	Results			
		Excellent	Good	Questionable	Failure
1. Staphylococcic infections					
Cellulitis	20	13	7	..	..
Abscess	13	4	9	..	..
Infected wounds	13	9	4	..	..
Infected burns	4	..	3	1	..
Ulcer with cellulitis	5	..	3	2	..
Subacute osteomyelitis	2	..	2	..	..
Postoperative parotitis	2	2	..	..	..
Carbuncle	1	1	..	..	..
Furunculosis	1	1	..	..	..
Hydroadenitis suppurativa	1	1	..	..	..
Acute mastitis	1	1	..	..	..
2. Hemolytic streptococcic infections					
Cellulitis	4	2	1	1	..
Septicemia	2	1	..	..	1
3. Pneumococcic infections					
Septicemia	1	1	..	..	..
Postoperative pneumonia	4	3	1	..	..
4. Mixed infections					
Deep abscess of neck	3	2	1	..	..
Postoperative wound infection	1	..	1	..	..
Subphrenic abscess	3	..	1	2	..
Peritonitis	3	..	..	3	..
Acute cholecystitis	2	..	1	1	..

or four hourly injections on the basis of previous experience.[1b] An arbitrary classification of the clinical results obtained with this dosage schedule is given in the table.

A satisfactory chemotherapeutic result was obtained in 95 per cent of the 63 selected cases of staphylococcic infection. The response followed the pattern that we have learned to expect from penicillin with a lag of twenty-four to seventy-two hours preceding any obvious clinical change, spontaneous resolution in the early cases and control of the invasive characteristics and localization in the later cases (figs. 5 and 6).

In general, the streptococcic infections were of relatively greater severity than the others. In 1 instance of hemolytic streptococcic cellulitis of the leg with septicemia, the process failed to respond to a dose of 100,000 units every eight hours for forty-eight hours and, likewise,

did not respond to a dose of 100,000 units every three hours. In another, the result was questionable since sulfadiazine was administered simultaneously.

The small number of pneumococcic infections reacted well to this plan of treatment in every instance.

As was expected, the results obtained in the 12 cases of mixed infections, produced by several or more bacterial species of both the gram-negative and gram-positive varieties, were questionable in 50 per cent of the cases.

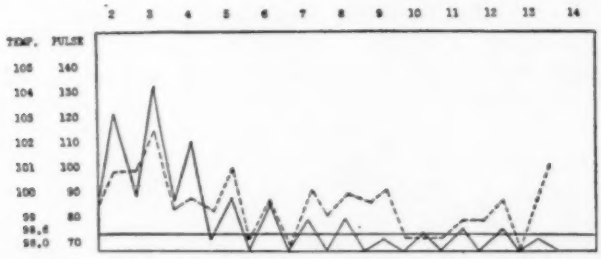


Fig. 5.—Graph of results in a 32 year old Negro women with an infected laceration of the forehead and extensive cellulitis of the face treated successfully with 100,000 units of penicillin every eight hours. The culture showed hemolytic streptococci, nonhemolytic streptococci and Corynebacterium pseudodiphthericum. The horizontal row of figures at the top shows the days of illness. The unbroken line indicates the temperature (Fahrenheit) and the broken line the pulse rate.

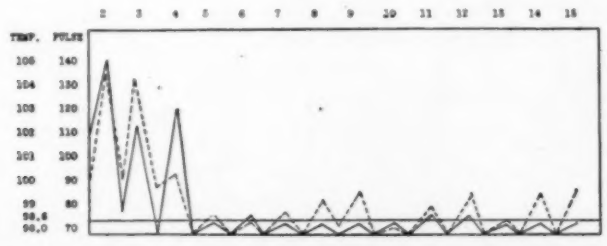


Fig. 6.—Graph of results in a 25 year old Negro woman with acute interstitial mastitis of the left breast, associated with chills, fever, headache and malaise. Complete control and spontaneous resolution of the infection occurred with chemotherapy with 100,000 units of penicillin every eight hours. The horizontal row of figures at the top shows the days of illness. The unbroken line indicates the temperature (Fahrenheit) and the broken line the pulse rate.

COMMENT

Although this series is too small to permit any conclusions, it appears that the maintenance of a more or less constant blood level of penicillin is unnecessary for efficient treatment in human beings with a penicillin-susceptible infection of moderate degree. The effectiveness of the various methods of administration which unquestionably maintain at

least a therapeutic concentration is well established, but the injection intramuscularly every eight hours of 100,000 or more units of penicillin in aqueous or isotonic sodium chloride solution seems to be an efficient substitute method. The inhibition of growth of susceptible bacteria in vitro after temporary exposure to penicillin may also occur in clinical infections. In our series of selected cases in which no detectable levels often occurred for five hours out of every eight during treatment, the results obtained were indistinguishable from those with established methods.

The advantages of an eight hour dosage schedule using aqueous penicillin are obvious, the chief ones at the present time being the decreased time and labor required by nursing personnel and the lessened discomfort and inconvenience to the patient. Without considering the time required to prepare penicillin and sterilize needles and syringes, some idea of the added burden which the three hour method has brought to the nurses can be gained from a recent survey made at the Cincinnati General Hospital. On one ward of 31 patients, 18 were receiving penicillin every three hours, requiring a total of one hundred and forty-four intramuscular injections each day. The administration of only three or two injections to each patient every twenty-four hours would release an appreciable proportion of the nurses' time for other more necessary or possibly neglected duties. When the hours of injection are fixed at 7 a. m., 3 p. m. and 11 p. m., it is possible for the patient to have a good night's rest with uninterrupted sleep. Needless to say, the method has been popular with both patients and nurses during our study.

Because of the possibility that bacteria might develop increased resistance to penicillin under this plan of treatment, studies have been started to detect any tendency in this direction.

Until further experimental information is gathered, the eight hour schedule with an augmented dose is recommended only in penicillin-susceptible infections of moderate degree, while in relatively resistant, severe or fulminating infections, the two or three hour schedule is still advised.

DISCUSSION

DR. ALEXANDER BLAIN III, Detroit: I would like to comment on Dr. Altemeier's paper in regard to penicillin dosage, with particular reference to infections of intestinal origin. It has long been said that penicillin is not effective against gram-negative organisms. This has been a great stimulus to investigation of streptomycin in infections of the intestinal tract. It has been found, however, in work on dogs (Harper, W. H., and Blain, A., III: The Effect of Penicillin in Experimental Intestinal Obstruction: Preliminary Report on Closed Loop Studies, *Bull. Johns Hopkins Hosp.* **76**:221-244 [June] 1945. Blain, A., III: Penicillin in Experimental Intestinal Obstruction: A Summary of Observations with Reference to Their Clinical Application, *Surg., Gynec. & Obst.* **84**:753-758 [April] 1947), that penicillin is effective for all practical purposes over a short

period of time against Escherichia coli and other inhabitants of the intestinal tract. This fact is of importance clinically in acute mechanical intestinal obstruction or strangulated hernia. It should be remembered that in cases of intestinal obstruction in which bowel strangulation is suspected, or cannot be ruled out, penicillin in massive doses should be given. You are probably all familiar with the original experiments at Johns Hopkins Hospital with penicillin in the treatment of syphilis. When first studied, the dosage of penicillin was too low and it was thought to be of no value in this disease. Later investigations, with larger dosages, revealed that penicillin was effective against syphilis. The same thing is true of infections originating in the intestinal tract and general peritonitis of such origin, as demonstrated in human beings by Dr. George Crile Jr.

I enjoyed the paper very much and believe that Dr. Altemeier's studies are a distinct contribution in the clinical use of penicillin in such diseases as pneumonia, subacute bacterial endocarditis and gonorrhea. In treating bowel strangulations however, all previous ideas on dosages should be abandoned. Massive amounts (up to 1,000,000 units every three hours) should be administered prior to and for a day or more after resection of the bowel and release of the obstruction. Dr. Altemeier's revised dosage schedule with prolonged intervals between injections of penicillin would not yet apply to this situation, because we know nothing of minimum effective dosage for bowel strangulation or peritonitis.

MINDLESSNESS AND GENERALIZED SPASTIC PARALYSIS FOLLOWING CYCLOPROPANE ANESTHESIA

Sequelae in a Child with Acute Appendicitis

E. LEE STROHL, M.D.
AND
FRANCIS E. SARVER, M.D.
CHICAGO

IT IS NOW one hundred and two years since ether was used for a surgical operation.[1] During this time many anesthetic agents have been developed and used clinically. In spite of the advances in the field of anesthesiology, complications of anesthetic agents still occur.

Convulsions which develop during an operation are frequently the first sign of a serious, and occasionally fatal, complication. The problem of convulsions during anesthesia has been primarily the concern of the anesthetists. It has become increasingly evident, when convulsions occur, that many factors in the care of the patient prior to operation, during operation and following operation, are the responsibility of the surgeon.

The subject was introduced in England in 1927 by reports of Wilson[2] and Pinson.[3] Several reports of isolated cases followed. Since the convulsions occurred during the administration of ether, they were called "ether convulsions." It is now known that this complication is not related solely to any specific property of ether. Convulsions followed by cerebral complications may result from the administration of other anesthetic agents. In 1937, Lundy[4] reviewed 144 cases from the literature. He listed a large number of causative factors. His study revealed a mortality rate of 18.9 per cent.

From the Departments of Surgery, St. Luke's Hospital, Chicago, and the University of Illinois College of Medicine.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

1. Bigelow, H. J.: Insensibility During Surgical Operations Produced by Inhalation, Boston M. & S. J. **35**:309-317 (Nov. 18) 1846; Ether and Chloroform: A Compendium of Their History, Surgical Use, Dangers, and Discovery, Boston, David Clapp, 1848.

2. Wilson, S. R.: Ether Convulsions, Lancet **1**:1117-1119 (May 28) 1927.

3. Pinson, K. B.: Convulsions Occurring During Surgical Anesthesia, Brit. M. J. **1**:956-958 (May 28) 1927.

4. Lundy, J. S.: Convulsions Associated with General Anesthesia, Surgery **1**:666 (May) 1937.

Convulsions occurring during administration of nitrous oxide, followed by postoperative encephalopathy and death, are generally accepted as due to anoxemia and cerebral anoxia. However, anoxia [5] in all probability is a major factor in convulsions during other forms of inhalation anesthesia.

In addition to the occurrence of convulsions, there are other less frequent complications and sequelae of inhalation anesthesia: (1) sudden death under anesthesia, (2) delayed death, usually following a period of coma and repeated seizures, and (3) survival with permanent or transitory neurologic manifestations. Although instances of the latter type, namely, survival with permanent neurological damage are not common, more have occurred than are reported in the literature.

A case of permanent cerebral cortical damage and generalized spastic paralysis following cyclopropane anesthesia for appendectomy, has come to our attention. It is the subject of this report. A study of the literature reveals no similar sequelae of this particular anesthetic agent. Taylor's [6] report of 33,777 cases of administration of cyclopropane with convulsive movements in 39, or 0.1 per cent, indicates the safety of this agent when used by an anesthetist well trained in its use.

REPORT OF A CASE

C. R., a white girl, 7 years of age, previously in good health, was admitted to an outlying Chicago hospital on Aug. 5, 1947. For forty-eight hours prior to admission, the patient had suffered acute abdominal pain associated with nausea and persistent vomiting. Physical examination revealed an acutely ill child, who was dehydrated and dyspneic. There was considerable tenderness and muscle spasm in both lower quadrants of the abdomen, with rebound pain. The results of physical examination were otherwise negative. The oral temperature was 102 F. and the pulse rate 100. The white blood cells numbered 33,400 per cubic millimeter, consisting of 92 per cent polymorphonuclear leukocytes and 8 per cent lymphocytes. The red blood cells numbered 4,250,000 per cubic millimeter. The hemoglobin was 13 Gm. The past medical history was noncontributory, with no history of epilepsy or convulsive seizures occurring either in the patient or her immediate family.

A diagnosis of appendicitis, with perforation, was made. Morphine sulfate, ⅛ grain (0.008 Gm.), and atropine sulfate, 1/300 grain (0.0002 Gm.), were given preoperatively. Cyclopropane anesthesia was selected. The operation proceeded without incident until twenty minutes after the incision was made. At that time it was noted that unusual clonic movements of the face, arms, legs and abdominal muscles were present. The anesthetist reported that the patient was not "light." After removal of the appendix, the incision was closed and 1 grain (0.064 Gm.) of phenobarbital sodium was given intramuscularly. The convulsive movements became more pronounced and persisted for fifteen minutes. At this time the patient became cyanotic and respirations stopped. Artificial respirations

5. Courville, C. B.: Untoward Effects of Nitrous Oxide Anesthesia, Mountain View, Calif., Pacific Press Publishing Assoc., 1939.

6. Taylor, I. B.: Cyclopropane Anesthesia, with a Report of the Results in 41,690 Administrations, Anesthesiology **2**:641-653 (Nov.) 1941.

brought about spontaneous respiratory excursions in ninety seconds. The rectal temperature had risen to 106 F. The patient was sponged.

One and a half hours after the anesthesia was started, generalized convulsions were still present. The patient was placed in an oxygen tent. She received 1,000 cc. of 5 per cent dextrose in isotonic sodium chloride solution intravenously.

The postoperative course was characterized by fever with temperature ranging to 105 F. rectally. There were frequent intermittent convulsions. The convulsions persisted for forty-eight hours. For nine days there was alternate excitation and coma. The patient was admitted to St. Luke's Hospital on the ninth postoperative day, at which time she came under our observation.

At this time, the patient was quiet in bed, with occasional whining but no speech. She moved all parts of her body aimlessly. The corneal and pupillary reflexes were active, and the deep tendon reflexes were absent.

A lumbar puncture revealed normal clear spinal fluid under normal pressure. No cells were seen in the spinal fluid. The Ross-Jones reaction was negative, globulin reaction negative and the colloidal gold curve 0000000000. Blood cell counts and results of studies of the chemical content of the blood at this time were within normal limits.

Nutrition was maintained by tube feedings for three months. Aspiration pneumonia developed during this period and was successfully treated with penicillin, oxygen and parenterally administered fluids.

An electroencephalogram on December 5 revealed abnormally slow electroencephalographic waves, consistent with diffuse cortical damage, maximal in the parietal areas, with no evidence of epilepsy. Mental evaluation tests, three months postoperatively, revealed an estimated age of 5 to 10 months. There was no bowel or bladder control. Movements were uncoordinated and characterized by coarseness, spasticity, cog-wheel rigidity and weakness. The child could not stand or walk. She was discharged one hundred and thirty-six days after the onset of illness.

ANALYSIS OF CAUSATIVE FACTORS

Most authors agree that anoxia is the underlying factor in the occurrence of convulsions. Inasmuch as the cerebral cortical cells are more susceptible to anoxia than other tissues, the early development of convulsions is easily explained.

The physiologic classification of anoxemia, according to Barcroft,[7] indicates a number of factors which must be considered in each case. In anemic anoxemia, present in patients with lack of, or inactivation of, hemoglobin, the red cells carry less oxygen, although the oxygen tension in the blood may be normal. In stagnant anoxemia, because of slowed circulation, the oxygen supplied to the tissues is reduced. In anoxic anoxemia, the oxygen tension in the blood is lowered, so that there is actually less oxygen in solution, with a decrease in dissociation of hemoglobin. This type results in less available oxygen for tissue consumption. In histotoxic[8] anoxemia, the tissue cells of the body are less able to utilize the available oxygen due to drugs or toxins.

7. Barcroft, J.: Anoxemia, Lancet **2**:485 (Sept. 4) 1920.

8. McClure, R. D.; Hartman, F. W.; Schnedorf, J. G., and Schelling, V.: Anoxia: A Source of Possible Complications in Surgical Anesthesia, Ann. Surg. **110**:835 (Nov.) 1939.

A partial listing of the clinical factors which may result in the production of an anoxic state is found in the table, as given by Ray and Marshall.[9]

Factors Influencing the Anoxic State and Development of Convulsions During Anesthesia

Factors Pertaining to Individual Susceptibility
- Youth
- Female sex
- Convulsive diatheses

Factors Pertaining to the Anesthetic Agents
- Probable moderate anoxia incident to anesthesia
- Too deep anesthesia
- Combination of anesthetic agents
- Impurities in the anesthetic agent
- Impure oxygen
- Overoxygenation
- Too much or too little carbon dioxide
- Imperfections in anesthetic machine

Factors That Increase Oxygen Requirement of Body Tissues
- Fever
- Heavy blanketing of patient
- Overheated operating room
- Hot weather

Factors That Disturb Circulation of Blood
- Cardiac disease
- Vascular hypertension
- Vascular hypotension
- Cerebral vascular accident
- Reduced blood volume
- Hemorrhage

Factors That Disturb Respiratory Exchange
- Obstruction to air passages
- Faulty aeration of lungs
- Deficient alveolar absorption
- Poor position of patient on operating table
- Obesity

Factors Affecting Oxygen-Carrying Properties of the Blood
- Anemia
- Poisoning (as carbon monoxide)
- Methemoglobinemia

Factors Which Possibly Affect the Tissue Cells
- Ability specifically to utilize oxygen
- Acid-base disturbance
- Dehydration
- Hypoglycemia
- Calcium imbalance
- Nutritional deficiencies
- Sedatives, opiates, atropine
- Neurotoxin

In an analysis of the causative factors of the convulsions in this patient, one finds that the patient was a female child, with extreme dehydration and toxicity due to appendicitis with perforation. The United States Weather Bureau records for the day of operation reveal the Chicago temperature reading of 100 F. and the barometric pressure recording of 29.261 inches, or 743.2 mm. of mercury. Undoubtedly acidosis was present at the time of operation, in view of the history of persistent vomiting of forty-eight hours' duration. A possible source of further faulty oxygenation is found in the use of an adult type mask and tubing in this instance. Therefore a "dead space" was created in the closed system used with cyclopropane.

Prevention of the complications of anoxia during inhalation anesthesia consist of careful evaluation of the pulmonary, cardiovascular and

9. Ray, B. S., and Marshall, V. F.: Convulsions During General Anesthesia, Ann. Surg. **118**:130 (July) 1943.

renal systems of each patient prior to operation. Dehydration and acid-base imbalance should be corrected preoperatively by the proper parenterally administered fluids. Overheating of the patient and the operating room is to be avoided. Anemic patients should be given transfusions to achieve normal red cell and hemoglobin values. Preoperative medication should be individualized to prevent oversedation or undue excitement. The proper administration of the anesthetic agent is of primary importance. Prolonged operative procedures and undue trauma in the poor risk patient should be avoided.

With the occurrence of convulsions, it is necessary that one act quickly to correct the anoxia. The operation should be terminated promptly. The anesthetic should be discontinued. Oxygen should be administered, with the assurance that an adequate airway is open. Soluble barbiturates should be given to control the convulsions. Fluid and electrolyte balance must be maintained and compensation made for the blood loss. Hyperthemia may be allayed by sponging with water or alcohol or by fanning. When the convulsions are brought under control, the patient must be observed for signs of recurrence, oxygen therapy continued, the temperature kept below 102 F. and the electrolytes kept in balance by parenterally administered fluids.

SUMMARY AND CONCLUSIONS

Hypoxia, anoxia and convulsions may develop during any inhalation anesthesia. A case of permanent cerebral cortical damage following inhalation anesthesia, in which cyclopropane was administered, is described. The possible causative factors in the production of convulsions are discussed. Each factor may not be individually or solely responsible for the production of convulsions. However, these factors are all closely related to the transportation and utilization of oxygen for tissue consumption. This fact strongly suggests anoxia as the causative factor in the production of convulsions.

The development of this complication during inhalation anesthesia will be reduced by careful preoperative evaluation and proper preparation of the patient, proper selection and administration of the anesthetic agent and the elimination of contributory factors in the operative procedure. With the early recognition and the prompt and adequate treatment of hypoxia, the permanent damage which may result from cerebral anoxia can be avoided. The development of convulsive seizures demands prompt action in correcting the causative factors and the alleviation of the anoxia present.

DISCUSSION

Dr. John M. Waugh, Rochester, Minn.: Dr. Strohl and Dr. Sarver were kind enough to send their paper to me and I took the liberty of having Dr. Lundy review it. I know that his comments will be of interest to you, because he has been

interested in this problem for many years and probably has seen more of this complication than any of us. He felt that this case of Dr. Strohl's was a typical one of convulsions under general anesthesia, and I think that we should sincerely thank Drs. Strohl and Sarver for, first, emphasizing the condition under which this distressing complication is likely to arise and, second, pointing out that the condition is amenable to treatment when it is instituted early. Unfortunately, it will occasionally occur, as Dr. Lundy has pointed out, during anesthesia without any cause whatsoever in a patient in excellent condition. About five years ago I had 2 patients the same morning in the same operating room with the same team. Both had convulsions under general anesthesia, which were recognized and treated, and the patients suffered no untoward results. In both instances the operation was of considerable magnitude, and we were at a point where it would have been impossible to terminate the procedure. Dr. Lundy and Dr. Mousel pointed out in *Anesthesiology* in 1945 that they had been able to isolate from the nasopharynx in patients suffering convulsions in anesthesia a streptococcus organism which when inoculated in experimental animals produced spasms which were much severer under nitrous oxide and oxygen-ether anesthesia. Only further experimentation will prove whether this is significant. Lundy has observed that 3 cc. of 2.5 per cent "sodium pentothal" (sodium 5-ethyl-5-(1-methylbutyl) thiobarbiturate) given intravenously is sufficient to control the convulsions. I think that it is important for us all to point out to residents and interns in various hospitals where we are operating the fact that these convulsions do occur, even now with proper preoperative preparation, and it is extremely important to have "sodium pentothal" available for immediate administration.

MODERN SURGICAL TREATMENT OF ACUTE SUBDURAL ABSCESS

E. S. GURDJIAN, M.D.
AND
JOHN E. WEBSTER, M.D.
DETROIT

THIS is a study of 4 consecutive cases of acute subdural brain abscess successfully treated by surgical intervention and penicillin (table). Prior to the advent of chemotherapy and penicillin this fulminating condition was almost invariably fatal and was rarely diagnosed during life. Since the surgical management (drainage) has remained essentially unchanged, we must attribute this striking reduction in mortality to the use of antibiotics and sulfonamide drugs. In the next few paragraphs consideration will be given to a historical review of the condition, the structure of the subdural space, pathogenesis, pathologic aspects, clinical manifestations and treatment of the acute subdural abscess.

HISTORICAL REVIEW

In 1699 De LaPeyronie [1] performed the first successful operation for a subdural abscess. His patient sustained a head injury with fracture in the left parietal region and contusion of the overlying scalp. Although asymptomatic for twenty-five days, he began to show increasing visual weakness and disturbance of the conscious state. With trephining in the region of the original trauma, the dura was incised and 3½ ounces (about 99 Gm.) of pus was obtained from the subdural space. There was an extensive depression in the brain at the site of the purulent collection. During the following two months the patient made a complete recovery. De LaPeyronie reported this case ten years later, in 1709.[1]

Schmucker's patient [2] was a soldier who underwent trephining for a gunshot injury of the frontal lobe. "On the 19th day the dura mater

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 21, 1948.

From the Department of Surgery, Wayne University College of Medicine, and the Department of Neurosurgery, Grace Hospital, Detroit.

1. De LaPeyronie, F. G.: Mémoires pour l'histoire des sciences et des beaux arts, J. de Trevaux, 1709, p. 609.

2. Schmucker, S. L.: Vermischte chirurgische Schriften, Berlin, F. Nicolai 1776, vol. 1, p. 283, cited by Gross.[4]

Four Cases of Subdural Abscess (No Deaths)

Case No.	Age	Sex	Cause	Site	Organism	Associated Intracerebral Abscess	Meningitis	Convulsive Seizures				Encephalography	Follow-Up Period, Mo.
								Preoperative		Postoperative			
								Jacksonian	Generalized	Jacksonian	Generalized		
1	17	F	Chronic sinusitis	Left frontoparietal	No growth	None	No	Yes	Yes	No	No (26 mo.)	Not done	26
2	33	M	Chronic sinusitis	Right frontoparieto-occipital; left frontoparietal	Gram-positive cocci	Right frontal lobe	Yes	Yes	Yes	No	Yes (52 spells in 1947)	No subarachnoid air on affected side	22
3	27	M	Acute sinusitis	Right frontoparietal	Nonhemolytic streptococci	None	No	Yes	Yes	No	Yes; good control with "dilantin" and phenobarbital	Not done	14
4	25	M	Acute sinusitis; frontal osteomyelitis	Left frontoparietal	Hemolytic streptococci	Left parietal	Yes	Yes	Yes	No	Yes; good control with "dilantin" and phenobarbital	No subarachnoid air on affected side	7

rose into the trephine hole and fluctuated. A small puncture was followed by the escape of two ounces of whitish lymph; and 3 days subsequently, the delicate opening having closed, a crucial incision gave vent to an ounce of similar fluid. The man recovered." Guthrie [3] operated on 2 patients after the battle of Toulouse by incision of the dura and evacuation of pus. One patient died. In the Crimean War, Gross [4] cited examples of "operation for abscess of the cavity of the arachnoid" by Cowan,[5] Demme [6] and Pirogoff.[7] The latter's patient lived.

In civilian life Mursinna [8] "removed three circles of the occipital bone and opened the dura mater with the effect of giving vent to a very offensive yellowish fluid." Dumville [9] in 1858 treated a patient in Manchester Royal Infirmary for

> . . . a scalp wound and denudation of the frontal bone. The symptoms first made their appearance 3 weeks after the accident, and led to the supposition that matter had formed between the bone and the dura mater. The trephine was applied; no matter was found on the dura mater, which however, was whiter and thicker than usual except at one point of the margin of the trephine hole, where there was a red spot; this proved to be a small hole in the dura mater, into which the flat end of a probe was passed, whereupon a quantity of most offensive matter spurted out. The symptoms were relieved and the patient ultimately got well.[10]

Watson [11] in 1870 treated a child aged 8, "in whom symptoms of phrenitis followed a blow on the forehead from a piece of road metal." A fistula developed in the left frontal bone. "Whenever the opening closed, the child became unconscious and convulsed, but she was free from symptoms at other times. A crucial incision of the dura mater, after trephining, permitted escape of a wine glassful of pus."

---

3. Guthrie, G. J.: Injuries of the Head Affecting the Brain, London, J. Churchill & Sons, 1842.

4. Gross, S. W.: An Examination of the Causes, Diagnosis and Operative Treatment of Compression of the Brain, as Met with in Army Practice, Am. J. M. Sc. **66**:40-74 (July) 1873.

5. Cowan, in Williamson, G.: Military Surgery, London, J. Churchill & Sons, 1863, p. 36, cited by Gross.[4]

6. Demme, H.: Militär-chirurgische Studien in den italienischen Lazarethen von 1859, Würzburg, 1861, vol. 2, p. 74, cited by Gross.[4]

7. Pirogoff, N. I.: Grundzüge der allgemeinen Kriegschirurgie, Leipzig, F. C. W. Vogel, 1864, cited by Gross.[4]

8. Mursinna, C. L., cited by Gross.[4]

9. Dumville: Brit. M. J. **2**:743, 1858; cited by Gross.[4]

10. Holmes, T.: System of Surgery, vol. 1, revised by J. H. Packard, Philadelphia, Henry C. Lean's Son & Co., 1881.

11. Watson, P. H.: Case of Intracranial Abscess Following Injury Successfully Treated by Trephining, Edinb. M. J. **16**:43, 1870.

MacEwen's [12] results in the treatment of intracerebral abscess are well known. He also recognized the occurrence of subdural abscess and reported 4 patients whom he treated by means of mastoidectomy and evacuation of the pus. He was impressed by the associated "ulceration of the brain" in connection with this lesion. He stated:

> . . . an abscess may form between the pia mater and the dura, being circumscribed by the adhesion formed between these two membranes. In such cases there is superficial inflammation of the brain, and not infrequently this results in brain ulceration, the molecular disintegrating products of which accumulate between the brain and the dura. Under these circumstances the plastic exudate formed on the inner side of the dura softens and degenerates; the membranes participating in the softening may become eroded and even perforated, so that pus may escape on the external surface of the dura or in the case of an osseous perforation, through the tegmen tympani.

Three of the 4 patients treated survived.

The textbooks on surgery by Holmes [10] and Gross [13] described subdural abscess as "an effusion of pus into the arachnoid sac." They stated that when the skull is trephined the dura immediately rises, the pink silvery hue of this membrane is lost and its pulsations are absent. These are characteristic observations in accumulation of pus beneath the dura mater according to these authors.

In reviewing the case histories of the patients described in the preceding paragraphs, it is apparent that a majority had abscesses of a traumatic origin and in some cases fistulous communications were described. Subdural abscess complicating mastoid infection has also been described. No record of successful operative management of the fulminating acute subdural abscess resulting from paranasal sinus disease was found in the consulted literature of the eighteenth and nineteenth centuries. However, many cases in which autopsy was done were reported (Richter in 1773,[14] Celliez in 1806,[15] Schutz in 1812,[16] Paulsen in 1861,[17] Carver in 1883 [18] and Wallenberg in 1885 [19]).

---

12. MacEwen, W.: Diseases of the Brain and Spinal Cord, New York, MacMillan & Co., Ltd., 1893.

13. Gross, S. D.: A System of Surgery, ed. 4, Philadelphia, Henry C. Lea, 1866, vol. 2.

14. Richter, A. G.: De morbis sinuum frontal, Gottingæ, J. C. Dieterich, 1773, cited by Courville.[34]

15. Celliez: Observation sur un absces dans le sinus frontal et dans le crane, accompagne de la paralysie de la paupiere superieure, et d'autres symptomes tres remarquables, J. de méd. et chir., pharm. **11**:516, 1806.

16. Schutz: Stirnhohlenabscess, Allg. med. Ann., 1812, p. 750; cited by Courville.[34]

17. Paulsen, J. P., cited by Courville.[34]

18. Carver: Acute Necrosis of the Orbit, Brit. M. J. **1**:1183, 1883.

19. Wallenberg, A.: Empyem des linken Sinus frontalis, Perforation nach der Schadelhohle hin, intradurale Eiterung, Neurol. Centralbl. **14**:903-908, 1895.

Monographs on the intracranial complications of paranasal sinus disease by Dreyfuss in 1896,[20] Kuhnt in 1895,[21] Killian in 1900[22] and Gerber in 1909[23] included observations on subdural abscess.

During the past fifty years sporadic cases of subdural abscess, usually resulting from otitis media and successfully treated surgically, have been described. Butler's[24] patient recovered after drainage of subdural pus and drainage of purulent lateral sinus thrombosis. One of the 2 patients reported by Gardner[25] recovered after drainage. Kubik and Adams[26] described 14 cases of acute subdural abscess with 2 recoveries; one of the patients that recovered was given sulfonamide drugs. Kahn[27] mentioned 12 patients with subdural abscess, with 2 recoveries. Glass[28] reported on a patient in whom extensive craniotomy was necessary before recovery. Penicillin was used in this case. Botterell[29] reported 2 patients with subdural abscess successfully treated surgically and with penicillin.

STRUCTURE OF THE SUBDURAL SPACE

The subdural space, which is a potential space, is bounded externally by dura mater and internally by the pia arachnoid.

The dura mater is composed of dense, fibrous and elastic tissues, lined on its inner surface by mesothelial cells. Blood vessels extend into the bone from the outer surface, and MacEwen[12] has pointed out that there is also a "wide meshed capillary network with peculiar

20. Dreyfuss, R.: Die Krankheiten des Gehirns und seiner Adnexa im Gefolge von Naseneiterungen, Jena, Gustav Fischer, 1896, pp. 12-29 and 64-67.

21. Kuhnt, H.: Ueber die entzundlichen Erkrankungen der Stirnhohlen und ihre Folgezustande, Wiesbaden, J. F. Bergmann, 1895.

22. Killian, G.: Die Thrombophlebitis des oberen Langsblutleiters nach Entzündung der Stirnhohlenschleimhaut, Ztschr. f. Ohrenh. **37**:343, 1900.

23. Gerber, P. H.: Die Komplikationen der Stirnhohlenentzündungen: Beitrage zur Anatomie und Klinik der Stirnhohlen, Berlin, S. Karger, 1909.

24. Butler, T. H.: Subdural Abscess, Thrombosis of the Lateral Sinus, and Diffuse Osteomyelitis of the Skull Bones Treated with Vaccines: Recovery, Brit. M. J. **1**:602-603 (March) 1912.

25. Gardner, W. J.: Subdural Abscess: Its Relation to Sterile Purulent Leptomeningitis, Ohio State M. J. **29**:235-238 (April) 1933.

26. Kubik, C. S., and Adams, R. D.: Subdural Empyema, Brain **66**:18-42 (March) 1943.

27. Kahn, E. A.: Acute Subdural Abscess, in Bancroft, F. W., and Pilcher, C.: Neurological Surgery, Philadelphia, J. B. Lippincott & Co., 1946, p. 88.

28. Glass, R. L.: Osteoplastic Flap Method in the Treatment of Subdural Abscess, J. Neurosurg. **4**:391-393 (July) 1947.

29. Botterell, E. H.: Radical Removal of Brain Abscess, presented before Detroit Academy of Surgery in Toronto, March 13, 1947.

dilatations near the inner surface of the cranial dura mater. Hence once pathogenic organisms penetrate into the wide meshed capillary network on the inner side of the dura mater the whole of the subdural space is open to invasion."

The dura is intimately adherent to the inner skull surface, particularly at the base, because of the irregularity of the bone surface and the various foramens present. This accounts for dural tear with fractures at the base of the skull and the possible ingress of infection into the subdural and subarachnoid spaces. The lining of the dura of the calvarium is loosely fixed to bone except at the suture lines. Consequently fractures of the cranial vault frequently fail to produce dural tears, lessening the hazard of infection. The adherence of the dura at the suture line is due to developmental factors in that "before suture closure the outer dural layer (internal periosteum) is directly continuous with the external periosteum." [30] The inner surface of the dura is smooth and glistening. "The subdural cavity of the base is prolonged a short distance outward along the roots of the various cranial nerves before it is obliterated by the blending of the dura mater with the sheaths of the nerves." [30]

The subdural potential space is continuous with the vertebral subdural cavity. The subdural space contains a small amount of fluid, enough to lubricate the inner dural and the outer arachnoid layers, which are both covered with mesothelial cells.

The arachnoid consists of fibers of connective tissue, weblike in organization, which is covered externally with a smooth layer of mesothelial cells. Internally the arachnoid consists of a series of fibrous tissue bundles, with cerebrospinal fluid flowing through the meshes. The subarachnoid cavity is also lined with mesothelial cells. The tissue is without nerves and contains no nutrient blood vessels. It passes from convolution to convolution, bridging the sulci. In places this membrane is intimately attached to the pia mater. The arachnoid villi penetrate the subdural space and the dura.

Vascular communications between scalp, skull, meninges and brain are numerous. The dural sinuses and the intracranial and diploic veins are without valves, thus permitting reversal of blood flow in the presence of an obstruction. Infection may proceed via both vessels and perivascular sheaths. In infection of the middle ear, thrombosis of the veins, due to inflammation of the mucous membrane, may extend to the vessels of the bone and eventually into those of the intracranial membranes and the venous sinuses.

---

30. Morris-Schaeffer: Human Anatomy, Philadelphia, The Blakiston Company, 1943.

PATHOGENESIS

Subdural abscess may be traumatic or nontraumatic in origin. A neglected compound fracture of the skull may become infected, with extension of the infection into the epidural space. The dural barrier in another instance may fail completely, and the invading organism may involve the subdural space or the subarachnoid space, or it may cause an intracerebral abscess or sinus thrombosis.

In the nontraumatic form, the subdural space may be invaded, with the subarachnoid space and the brain escaping infection, or they may all be concomitantly involved in varying degrees and at varying intervals. An intradural abscess, or pachymeningitis interlamellaris, may occur. But as Ballance [31] has stated, "these intradural collections are of greater pathological than clinical interest." In nontraumatic conditions the trend of events depends on chance, anatomic features of the affected skull and its contents, the virulence of the invading organism, the mode of invasion and the host resistance. While in traumatic conditions a contiguous tract of infection may exist, involving bone, dura, arachnoid and pia, in the nontraumatic types a commoner route of infection is by retrograde thrombophlebitis and perivascularitis.

The infection may enter the subdural space by direct or indirect routes or both. A direct route of infection, as has already been discussed, is seen in compound fractures of the skull or in some cases of mastoiditis. In the latter, a chronic abscess may form with involvement of dura and arachnoid and the eventual occurrence of ulceration of the brain surface or brain abscess. A similar direct extension of the infection may take place with paranasal sinus disease. Osteomyelitis and, in succession, dural, arachnoid and brain involvement may occur.

When involvement occurs by the indirect route, the infection may be transmitted by retrograde venous thrombosis and perivascularitis in the course of an acute or chronic paranasal sinus disease. Before time is allowed for mobilizing host resistance, a fulminating infection is produced in a period of days. A massive intracranial lesion in the subdural space or the brain, or both, may be produced. In others, there may be meningitis without massive suppuration.

Rare causes of subdural abscess are rupture of an intracerebral abscess into the subdural space and invasion of the subdural space in an infected scalp-skull malignant condition. In osteomyelitis of the skull, subdural abscess is seen occasionally (fig. 1). McKenzie [32] reported 2 instances of subdural abscess among 48 patients with osteomyelitis of the skull.

---

31. Ballance, C. H.: Surgery of the Temporal Bone, London, MacMillan & Co., Ltd., 1919.

32. McKenzie, D.: Diffuse Osteomyelitis from Nasal Sinus Suppuration, J. Laryng., Rhin. & Otol. **28**:6 and 129, 1913.

PATHOLOGIC ASPECTS

The microscopic and macroscopic pathologic characteristics of subdural suppuration have been discussed in detail by Courville and Blomquist,[33] Courville [34] and Kubik and Adams.[20] The production of the subdural abscess has been compared to a localization of pleurisy which occurs "by that adhesive inflammation which sometimes solders the visceral and parietal layers of the pleura." [12] The inflammatory reaction and the products therefrom in the subdural space are isolated in a portion of the space by a process of adhesion of the subjacent arachnoid to

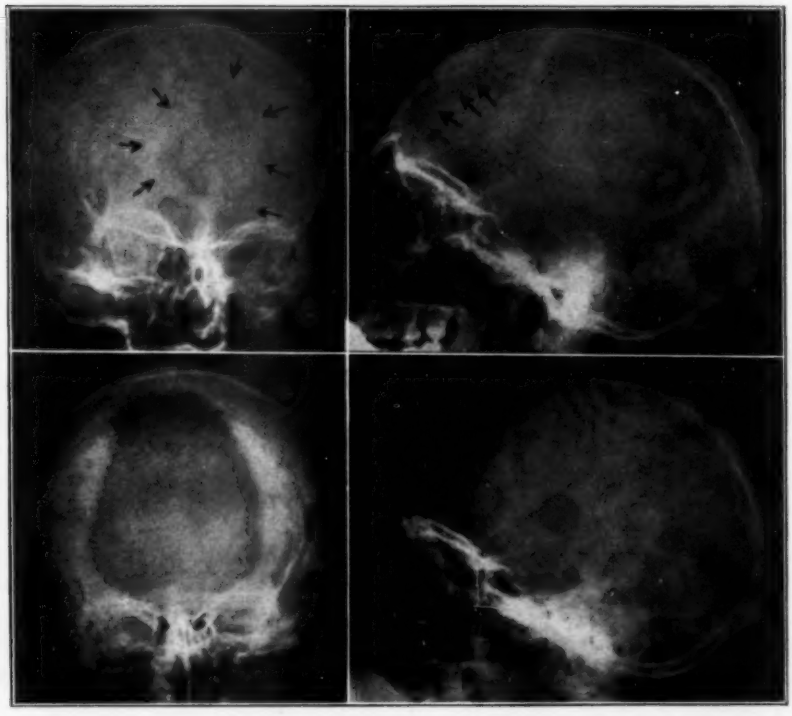


Fig. 1.—The two upper roentgenograms show the extent of the osteomyelitis of the frontal bone in case 4. The two lower roentgenograms show the area of bone removed. In the lateral view the trephine opening for the drainage of the subdural abscess on the left side may be seen.

the inner dura. This is particularly true in the more chronic form of subdural abscess. A neomembrane may form to limit and loculate the subdural collection. The presence of this membrane may explain why earlier descriptions of subdural space abscess spoke of "abscess of

33. Courville, C. B., and Blomquist, O. A.: Traumatic Pachymeningitis Interna and Subdural Abscess, Arch. Surg. **42**:890-908 (May) 1941.

34. Courville, C. B.: Subdural Empyema Secondary to Purulent Frontal Sinusitis, Arch. Otolaryng. **39**:211-230 (March) 1944.

the cavity of the arachnoid." Courville and Blomquist [33] described the pathologic features in 5 cases of traumatic subdural abscess. They pointed out that "a subdural abscess is characterized by the presence of variable amounts of fibrinopurulent or purulent exudate in the subdural space, most of which escapes when the dura is opened at operation or at autopsy." The exudate is collected over "the upper and anterior portions of the hemisphere." In advanced stages the collection extends from "near the frontal pole to as far back as the occipital pole." At times the pus collects between the falx and the medial aspects of the hemisphere. The arachnoid appears to be a good barrier to the extension of the infection into the subarachnoid space. The cerebral sulci are widened and the convolutions ridged; the cortex is depressed to varying degrees; the subarachnoid space is obliterated, and the ventricular system is distorted. The cortical surface is usually reddened "incident to congestion and, at times, to focal subpial hemorrhagic extravasations giving the brain a mottled appearance," Subdural suppuration may be bilateral.

The microscopic observations showed inflammatory reaction on the inner dural surface, with the dura only slightly invaded. Thrombosed veins are noted, and thrombosis of the superior longitudinal sinus or the lateral sinus (with otitis media) frequently accompany subdural abscess. After healing, it was noted that the dura, the leptomeninges and the cortex were bound together by firm fibrous adhesions.

CLINICAL MANIFESTATIONS

The clinical manifestations vary with the acute and the chronic forms of the disease. In the acute form typical of the cases reported in this paper, a fulminating disease is encountered. Soon after the onset of acute sinusitis or during a chronic infection, and occasionally in the course of chronic or acute otitis media, there may suddenly appear evidences of profound intracranial disease. In 2 of the 4 cases described, probing or manipulation of the frontal sinus in chronic sinus disease preceded the onset of intracranial symptoms.

Severe headaches, with drowsiness, eventuating in stupor, may occur. Convulsive seizures, frequently jacksonian and meningismus with increased cerebrospinal fluid pressure, may be early observations in this condition. The white blood cell count may be elevated. Focal phenomena occur early. Aphasia, weakness or paralysis of the face and arm or one half of the body develops. There may be papilledema. It should be considered that the presence of meningitis with associated neurologic signs does not rule out a subdural abscess. It is important to consider that in subdural abscess signs and symptoms develop in two to five days from the time of onset of the intracranial complication.

The diagnosis should be considered in patients with paranasal sinus disease and ear infection who suddenly present evidences of intracranial involvement. Recognition of the possibility of a subdural abscess is the first step in the diagnosis of this condition.

In 2 of the 4 cases presented in this paper there were associated parenchymatous abscesses. Although both patients showed improvement after the subdural abscess was drained and penicillin instilled, both relapsed in four to seven weeks with the reappearance of symptoms, indicating intracranial involvement. An abscess of the right frontal lobe was excised in 1 case, and a left frontotemporal abscess was repeatedly

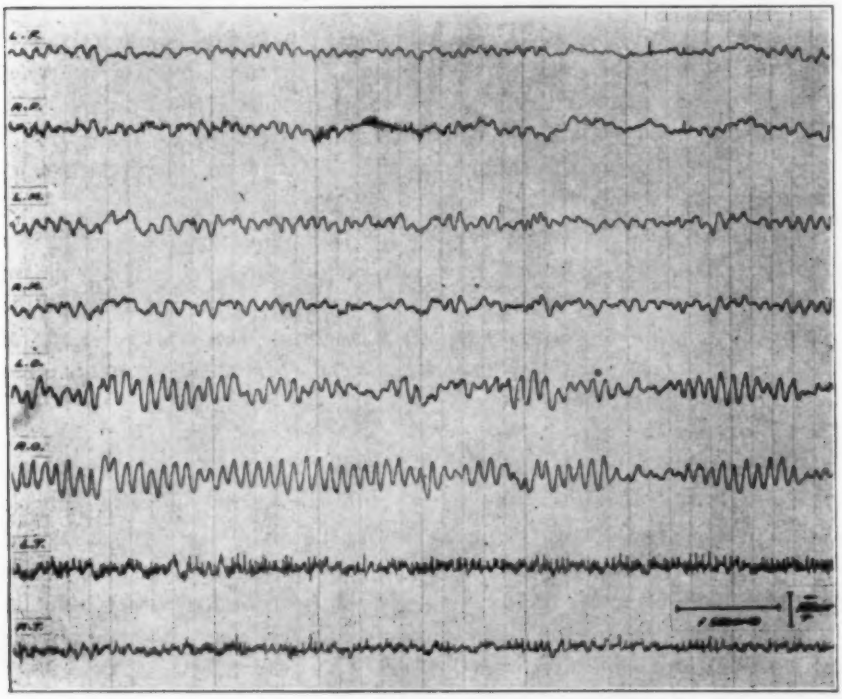


Fig. 2.—Electroencephalographic record in case 1 twenty-four months after evacuation of subdural pus. The record is essentially normal, although some slow activity may be noted in the left motor region. As of the date of writing, this patient had had no epileptic spells since discharge from the hospital.

tapped with penicillin instillation in the second patient. The question arises as to when the cerebral parenchyma was infected. Did this happen at the same time the subdural abscess was initiated, or did the cerebral abscess result from latent retrograde thrombophlebitis due to the subdural abscess? As has been pointed out before, acute subdural empyema is a fulminating disease which makes itself evident in the course of a week or less. A cerebral abscess, on the other hand, is usually more chronic, and with antibiotic and sulfonamide drug therapy it may continue to progress slowly for several weeks and encapsu-

late. Eventually signs of increase in intracranial pressure supervene because of the presence of an intracerebral mass, and unless this is drained or excised the patient's condition steadily grows worse. It is our impression that in our patients the pathogenesis of infection occurred simultaneously, for the cerebral and the subdural suppuration. Both of these patients returned to the hospital after a period of time which is usual for incubation in brain abscess.

The chronic form of subdural abscess may be associated with penetrating wounds, with patent craniodermal fistulas, untreated compound

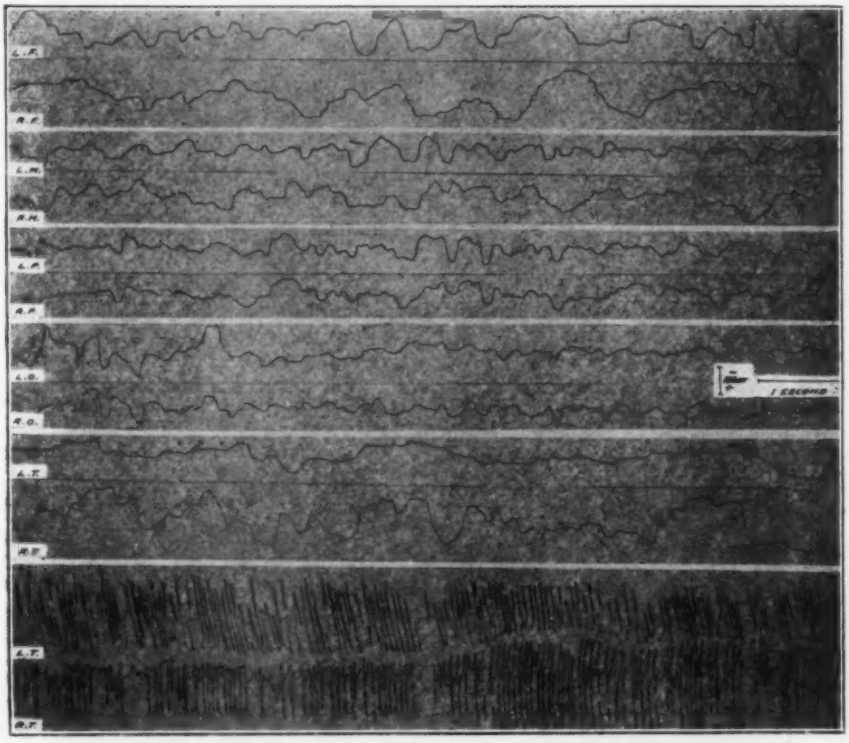


Fig. 3.—Electroencephalographic record in case 2 with bilateral subdural abscess. During the recording the patient had a spell as noted on the bottom electroencephalogram record. Pronounced involvement of the cortex bilaterally may be noted. This patient had fifty-two seizures during 1947.

fractures and in chronic and acute ear infection with mastoiditis. In the untreated patient with mastoiditis such an infection involves the subdural space by direct extension. The cases described by MacEwen [12] belong in this group. It is likely that such occurrences are now rare because of the modern plan of management of mastoiditis. Occasionally a chronic form of subdural abscess results from paranasal sinus disease. Before the era of penicillin and sulfonamide drug therapy, many of the

subdural abscesses in patients who survived after surgical management belonged in this category.

The presence of a subdural abscess should be suspected in patients with osteomyelitis of the skull presenting symptoms of intracranial involvement. In case 4 of our group there was an extensive osteomyelitic infection of the frontal bone. The subdural space on the left side was explored through a clean opening in the frontotemporal region of the skull not invaded by the osseous infection. McKenzie [32] discussed 2

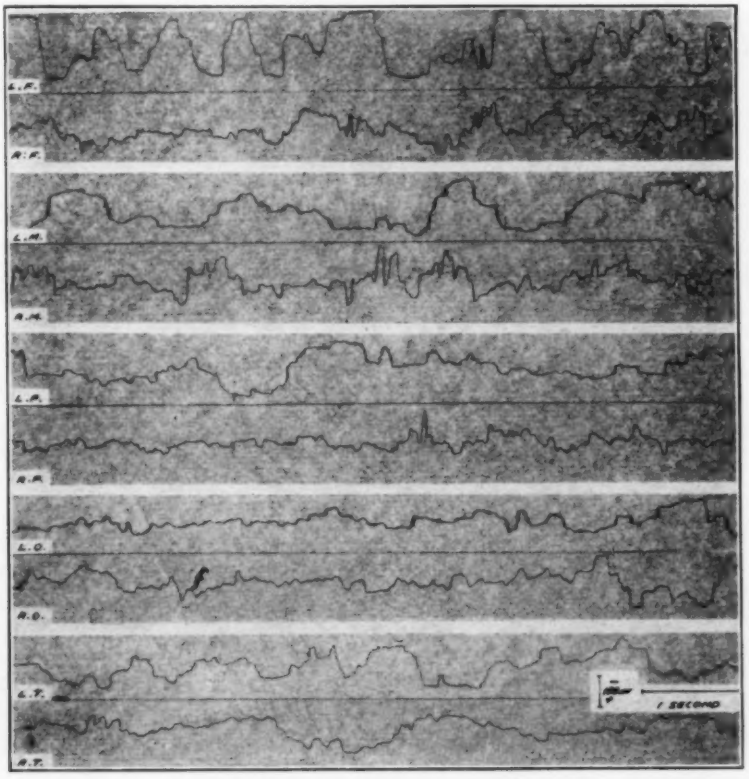


Fig. 4.—Electroencephalographic record (case 4), taken at the time of the acute stage of the disease, showing pronounced delta activity in the left frontoparietal region. The electrocorticogram shows disorganization bilaterally and from all leads.

cases of subdural abscess in 48 cases of osteomyelitis of the skull secondary to inflammatory disease of the nasal sinuses. It is likely that this incidence is rather low and that subdural abscess complicates osteomyelitis of the skull more frequently.

Carcinoma of the scalp has been observed to invade the skull, producing large areas of necrosis and sequestration. The dura may be exposed. The subdural space becomes infected. There may be both

subdural and cerebral abscesses, as we have seen in 2 patients. Such complications arise from direct extension of the infection or by perivascularitis and retrograde thrombophlebitis.

TREATMENT

The surgical treatment, sometimes emergency operation, is mandatory, and the patients do not survive without drainage of the pus and the instillation of penicillin. This can be done with little trauma to the brain and the meninges by simple trephination of the skull, incision of the dura and evacuation of the pus. The subdural space may be

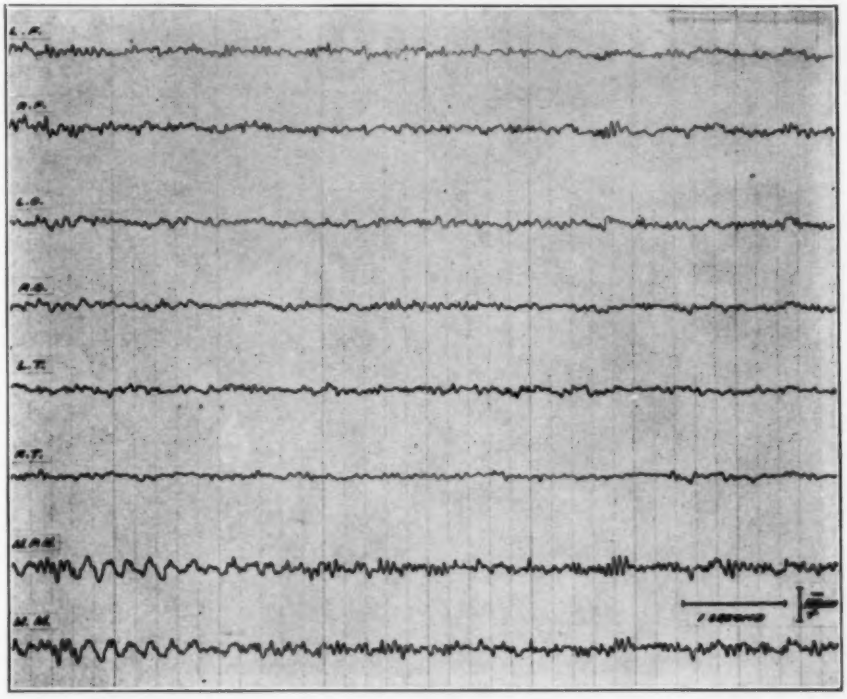


Fig. 5.—Electroencephalographic record (case 4) taken six months after that shown in figure 4, showing decided improvement in the pattern, but slow activity may be noted in the motor areas bilaterally, particularly on the left side. This record is suggestive of epilepsy, but the patient was well controlled with dilantin ® (sodium diphenyl hydantoinate) and phenobarbital.

irrigated with saline and penicillin solution. In extensive collections more than one burr hole may be made. Both sides are explored so that bilateral involvement may not be overlooked. Ideally, trephine openings should be made in the frontal, parietal and occipital areas bilaterally, but this may not be feasible in the desperately ill patients. Soft rubber catheter drains were used in 3 cases, and although no purulent material drained from them, they served as a means for the

introduction of the penicillin solution into the subdural space. This was done daily for three days. In the case in which drainage was not done the wounds were reopened and the subdural spaces inspected and penicillin instilled. Twenty-five thousand to 50,000 units of penicillin was injected in the initial exploration and 10,000 units thereafter. A total of two subdural injections was made in case 1 and four injections in the remaining 3 cases.

Penicillin was used systemically alone in 1 case, and penicillin and sulfadiazine were used together in the others. The dosage of penicillin varied from 20,000 to 100,000 units every three hours and that of sulfadiazine from 4 to 6 Gm. daily. In the 2 cases of meningis-

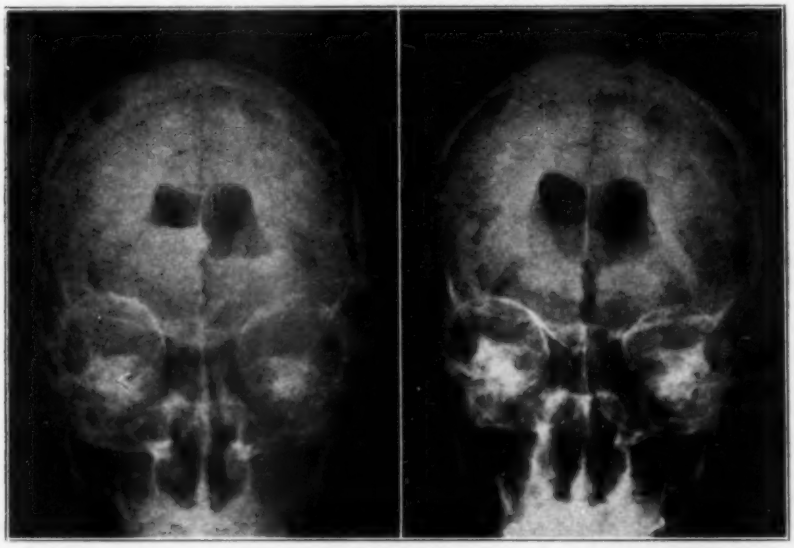


Fig. 6.—Air encephalograms in case 3. The encephalogram to the left was obtained on Jan. 30, 1947, before the patient was discharged from the hospital and after drainage of the subdural abscess. There is lack of aeration over the periphery of the brain on the right side. The air study to the right was obtained a year later (Feb. 4, 1948), showing the same lack of air in the subarachnoid spaces of the right frontoparietal region. These records justify the conclusion that there is arachnoiditis of a permanent nature over the right frontoparietal region.

mus, penicillin in doses of 10,000 units was administered intrathecally every day for three days and less frequently thereafter.

In the case of uncomplicated disease improvement after operation is rapid except that convulsive seizures may be frequent in the immediate postoperative period. If improvement is not rapid, further exploration is indicated. In case 2 the patient was little improved after evacuation of bilateral subdural abscesses. Reexploration revealed more purulent material in a more posterior position on the right side.

The importance of removal of the original focus either at the same time or preceding the surgical management of the intracranial compli-

cation cannot be overemphasized. Empyema of the paranasal sinuses, osteomyelitis of the skull, suppuration of the mastoid or the lateral sinus should be eradicated. In this group, 2 patients had preceding exenterations of the frontal sinuses. In another, the osteomyelitic portion of the skull was surgically removed and the subdural abscess simultaneously drained.

In cases 2 and 4, although decided improvement followed the evacuation of the subdural pus, frontal lobe abscesses were eventually excised

Fig. 7.—Air encephalogram showing lack of subarachnoid air over the left frontoparietal region in case 4.

and drained, respectively. The abscess in the left frontotemporal region (case 4) was repeatedly tapped with penicillin instillation. That of case 2, in the right frontal region, was excised because of the location and the degree of encapsulation. After excision of such a mass, adequate amounts of penicillin were injected subdurally to combat any remaining infection.

SEQUELAE

The most undesirable sequelae among these patients thus far have been convulsive seizures (fig. 2). All had convulsions prior to the

operative treatment. Three had immediate postoperative convulsive seizures and periodic convulsions after leaving the hospital (figs. 3, 4 and 5). (Three patients were working as of the date of writing.)

The degree of cerebrodural cicatrization and the proximity of the postinflammatory tissue to the motor area are related to the extent and severity of this complication. The earlier the diagnosis is made and surgical treatment instituted, the greater the likelihood of evacuating a more limited collection near the frontal pole. Earlier intervention may thus be of some aid in combating this undesirable sequela. Two of the 4 patients have had postoperative air studies. Both have shown arachnoiditis on the affected side, as evidenced by lack of aeration of the subarachnoid spaces. In 1 case the air studies were repeated, confirming the observation (fig. 6). These observations argue in favor of the presence of cerebrodural scars (fig. 7). It is of note that in 2 cases the surface of the brain was inspected preliminary to tapping for a brain abscess in one and excision in another. There was no evidence of macroscopic cerebrodural scarring such as described in postmortem observations.[34]

SUMMARY

Subdural abscess may be successfully treated by surgical evacuation and local penicillin instillation into the subdural cavity. Subdural abscess of paranasal sinus origin may be a fulminating and rapidly fatal infection. Early diagnosis and treatment are necessary for a successful result. Convulsive seizures are serious sequelae. Three of 4 patients in this group had this complication. Surgical treatment consists of trephine openings in the frontal parietal and occipital regions bilaterally, with the instillation of penicillin after evacuation of the purulent collection.

CYSTIC DISEASE OF THE LUNG

EDWARD J. McGRATH, M.D.
AND
MARCUS J. MAGNUSSEN, M.D.
CINCINNATI

IN 1925, Koontz [1] published the first description of cystic disease of the lung to appear in American medical literature. Since then, wide interest has developed in this condition, not only as a distinct pathologic entity in itself but more particularly as a significant factor in the differential diagnosis and treatment of clinical intrathoracic problems. Articles on pulmonary cystic disease are appearing with increasing frequency, and, what is probably of greater significance, large series of cases of this disturbance have recently been reported.[2] As emphasized by Adams,[2a] failure to recognize the frequency of cystic disease of the lung in the past has been due largely to the fact that it was mistaken for a variety of other pathologic conditions of the lung. Attention was called forcefully to this masquerade by Maier and Haight [3] in 1940, Brown and Robbins [4] in 1944 and Adams [2a] in 1946. Nevertheless, the inherent difficulties associated with the diagnosis of pulmonary cystic disease especially when complicated by acute infection or its sequelae, and the frequency with which the correct diagnosis goes unrecognized for long periods of time during which the patient is partially or completely incapacitated, is subjected to repeated ineffectual operative procedures and, in some instances, suffers fatal complications, warrant the publication of further experience with this difficult problem.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20, 1948.

From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital.

1. Koontz, A. R.: Congenital Cysts of the Lung, Bull. Johns Hopkins Hosp. **37**:340-361 (Nov.) 1925.

2. (*a*) Adams, W. E.; Philips, F. J., and Hanni, J. W.: Congenital Cystic Malformation of the Lung, J. Iowa M. Soc. **36**:425-433 (Oct.) 1946. (*b*) Moersch, H. J., and Clagett, O. T.: Pulmonary Cysts, J. Thoracic Surg. **16**: 179-199 (April) 1947. (*c*) Klosk, E.; Bernstein, A., and Parsonnet, A. E.: Cystic Disease of the Lung, Ann. Int. Med. **24**:217-232 (Feb.) 1946.

3. Maier, H. C., and Haight, C.: Large Infected Solitary Pulmonary Cysts Simulating Empyema, J. Thoracic Surg. **9**:471-494 (June) 1940.

4. Brown, R. K., and Robbins, L. L.: Diagnosis and Treatment of Bronchogenic Cysts of Mediastinum and Lung, J. Thoracic Surg. **8**:84-105 (April) 1944.

CLASSIFICATION

There is as yet no unaninity of opinion regarding the causation, pathogenesis or classification of the various anatomic mutations of pulmonary cystic disease. Consequently, the nomenclature of the subject also is controversial. By connotation, however, such specific lesions as tuberculous cavities, parasitic and hydatid cysts and excavated carcinoma of the lung are excluded from consideration, and by definition cysts of the mediastinum, whether teratoid or dermoid, of bronchogenic or enteric origin, are also eliminated. Moreover, the relationship of so-called cystic bronchiectasis to the problem, as well as that of the so-called epithelialized chronic pulmonary abscess, if such an entity exists, is still a matter of conjecture.

Until more definitive study succeeds in clarifying these problems the relatively simple classification devised by Koontz,[1] and recently used by Moersch and Clagett [2b] as a basis for discussion, would seem most practical. Briefly, all pulmonary cysts are divided into two major groups: those arising from the bronchial tree and those of alveolar origin. The essential difference is that bronchogenic cysts have an epithelial lining on a base composed of some or all of the structural elements of bronchi. The epithelial lining, while characteristically composed of stratified columnar ciliated cells, may, as a result of metaplasia, be cuboidal or squamous or, in the face of violent suppuration be almost entirely destroyed. Cysts of alveolar origin, on the other hand, have no such epithelial lining. The walls of these are composed of alveolar cells compressed together. Bronchogenic cysts may be solitary or multiple. They may occur in any lobe or combination of lobes, unilaterally or bilaterally. A popular medical fallacy that cystic disease of the lung is invariably bilateral, however, has no basis in fact. The present report is concerned only with bronchogenic cysts. Cystic bronchiectasis has been excluded from consideration.

DATA IN FIFTEEN CASES

During the past five years in the Department of Surgery of the University of Cincinnati, we have encountered 15 patients with cystic disease of the lung. In no instance was the lesion an incidental discovery. These patients' problems were immediately related to their cystic disease. In 4 patients the difficulty was a relatively chronic one; in 6, there was a more or less acute crisis superimposed on a chronic process, and in 5 the patient was observed during the presenting acute illness.

The diagnosis in 2 of the 4 patients with obviously chronic disease was chronic empyema. One underwent drainage by wide rib resection and was asymptomatic except that there was a marsupialized cyst, the nature of which had not been recognized. The other patient had also been relieved by open thoracotomy, but the wound had closed and the so-called empyema had recurred. Severe diabetes mellitus had developed

in the interval. A secondary open thoracotomy had accomplished marsupialization of the cyst, and subsequent efforts to obliterate the "empyema" cavity by phrenic interruption and muscle implant had come to naught. The third patient with a chronic problem was asymptomatic when seen by us. Four years previously he had sustained a contusing injury to his chest in an automobile wreck. A hemothorax developed, which was allowed to reabsorb spontaneously. As the roentgenogram began to clear, the top of an ovoid mass protruded above the fluid opacity. This was interpreted as a pulmonary sarcoma and extensive radiation therapy instituted. Finally, the patient, in a paroxysm of coughing, expectorated several ounces of old blood, and subsequent roentgenograms demonstrated the cystic nature of the lesion. The fourth patient with chronic symptoms had previously been given a diagnosis of abscess of the lung with residual bronchiectasis. The nature of the disturbance was identified roentgenologically and corroborated with bronchograms.

Of the 6 patients with acute presenting symptoms, 3 were initially thought to have postpneumonic empyema. In each instance, however, the diagnosis was only tentative, because the clinical picture was mild, out of all proportion to the extent of the pathologic condition demonstrated roentgenographically. In each instance, our suspicions were confirmed when thoracentesis, with replacement of part of the purulent fluid, by air, was carried out and positional roentgenograms were made. Two patients with acute presenting symptoms were given diagnoses of abscesses of the lung. In 1, the initial diagnosis was pulmonary tuberculosis with cavitation. Failure to demonstrate tubercle bacilli after an exhaustive three month search forced abandonment of this diagnosis in favor of acutely active chronic abscess of the lung. The patient was subjected to five separate drainage procedures before the cystic character of the lesion was recognized. The diagnosis for the sixth patient with acute presenting symptoms was given by the first group of physicians in attendance as a diaphragmatic hernia. This diagnosis was replaced with one of empyema, and intercostal tube drainage was instituted. Postdrainage positional roentgenograms revealed the nature of the lesion.

The remaining 5 patients had histories of continuous or recurring illness of two to thirteen years' standing. Three had sustained one or more previous operative procedures, aimed at drainage of either empyema or pulmonary abscess (in 1 instance fifteen operations had been done). The fourth patient of this group came to our attention as the result of hemorrhage, the last and worst in a series ascribed to a so-called pulmonary abscess. The last patient was a sadly neglected child, 3½ years old, who had been severely ill for three of his three and a half years with unrecognized infected cystic disease of his entire right lung.

Of the 15 patients observed 6 were male and 9 female. Two of the women were Negro. Ages ranged from 3½ years to 50 years, distributed as shown in table 1.

Duration of symptoms varied from five weeks to thirteen years (table 2).

As indicated, in all cases it was complication of the cyst or cysts that brought the case to medical attention. The complication in 10 instances was acute infection, in 4 hemorrhage and in 1 trauma. Among the 6 patients manifesting evidence of acute infection of recent onset, it is worthy of note that in 4 there was an obvious discrepancy between the mildness of the clinical pattern and the extensiveness of the roentgeno-

TABLE 1.—*Age Distribution*

Age Group, Years	Number of Patients
0-10	5
10-20	2
20-30	1
30-40	5
40-50 (incl.)	2

TABLE 2.—*Duration of Symptoms*

Duration	Number of Patients
5 weeks-2 months	5
2 years	1
3 years	2
4 years	2
5 years	1
6 years	1
8 years	2
13 years	1

logic observations. These patients, with roentgenographic evidence of obliteration of half or more of one lung, had only low grade temperatures (99 to 101 F.) and slow pulse rates (80 to 100); they were restive and were difficult to keep in bed. A persistent fatiguing, but nonproductive, cough was the most prominent and distressing symptom. A similar observation has been made by Head.[5] Oddly enough, after manipulation, such as bronchoscopy or thoracentesis, these patients had spiking temperatures and were acutely ill for two or three days and then returned to their former status. On the other hand, in the other 2 patients with acute symptoms of recent origin the clinical picture was one of prostrating intoxication. Of the 4 patients with hemorrhage, in 3 the hemoptysis was mild and in 1 exsanguinating.

5. Head, J. R., in discussion on Maier and Haight,[3] p. 493.

Conditions for which these lesions had previously been mistaken are listed in table 3.

The operative procedures, other than simple thoracentesis, to which these patients were subjected prior to the recognition of cystic disease are shown in table 4.

A brief résumé of the criteria used in the roentgenologic diagnosis of cystic disease in these patients deserves mention. Cysts filled with air alone and those which had been evacuated by operative drainage appeared on roentgenogram as spherical or ovoid areas delineated by a thin but well defined opaque wall, beyond which the pulmonary tissue was comparatively normally translucent. Another item of significance

TABLE 3.—*Differential Diagnosis* *

Diagnosis	Number of Patients
Empyema	7
Pulmonary abscess	5
Tuberculosis (pulmonary)	1
Tuberculous empyema	1
Sarcoma of lung	1
Diaphragmatic hernia	1
Bronchiectasis	2

* In several patients, two previous diagnoses were entertained before the cystic nature of the lesion was recognized.

TABLE 4.—*Previous Surgical Procedures*

Trochar thoracostomy	5
Repeated open thoracotomy	5
Implantation of free fat graft	2
Schede unroofing thoracoplasty	1
Muscle implantation	2
Roentgen therapy	1

is that cysts tend to retain their spherical or ovoid contour in both anteroposterior and lateral projection of the chest, whether air bearing or fluid filled or both. When the fluid-filled cyst has been aspirated, we have found it helpful diagnostically not to attempt to evacuate fluid completely and to replace the fluid withdrawn partially with air. Then by positional roentgenologic studies, including lateral decubitus roentgenograms, it has been possible to outline the cyst satisfactorily. Finally, where the cystic nature of the lesion has not been obvious in routine roentgenologic studies, this fact has, on occasion, been demonstrated in bronchographic studies by the elongation and displacement of bronchi by the cyst. In only 1 patient in this series were we unable by one or another of the foregoing criteria to secure confirmatory evidence of the presence of cystic disease.

In 13 of the 15 patients, the diagnosis was established by microscopic demonstration of the epithelium-lined cyst wall. In the other 2, both of whom refused operative removal of the lesion, the diagnosis was based on the roentgenographic pattern of the cyst. In both of these, however, the cysts were drained, in 1 by catheter thoracostomy and the other by thoracentesis, these drainage procedures being intended as preliminary measures, to be followed by operative removal of the lesion. Among the 13 patients operated on, the cysts were removed by lobectomy or pneumonectomy in 11. There were eight lobectomies and three pneumonectomies. The cysts in the 2 remaining patients were marsupialized and as much of the wall excised as could be removed safely. One of these patients was severely diabetic, and her physician absolutely forbade so extensive an operative procedure as a lobectomy. The other patient had far advanced but quiescent tuberculosis in the underlying lung, with a quiescent lesion in the opposite apex. In the entire group of 15, cysts were found to be solitary in 10 and multiple in 5. The anatomic distribution is shown in table 5.

TABLE 5.—*Anatomic Distribution*

Distribution	Number of Patients
Right lung, upper lobe	0
Right lung, middle lobe	2
Right lung, lower lobe	8
Entire right lung	1
Left lung, upper lobe	2
Left lung, lower lobe	2

In the entire group, there were 2 deaths, both at operation. The first was of a 3½ year old child who had been desperately ill for three years with his right lung entirely cystic and grossly infected. An attempted pneumonectomy was undertaken, with great misgivings, as a procedure of desperation. The child died as the pneumonectomy was being completed. The second death was more tragic. This was of a 4 year old boy in whom a pulmonary cyst had been suspected but not demonstrated. Exhaustive efforts had been made to secure transbronchial drainage without success. Repeated attempts to aspirate the lesion transthoracically had also failed. During a six month period, every device had been used to arrest the lesion demonstrated by roentgenogram, in spite of which the child's physical condition deteriorated and the roentgenograms became progressively more opaque. A direct operative attack was finally decided on. Elaborate precautions were taken to provide for bronchial spillage. When the chest was opened, however, there was a sudden overwhelming gush of foul, putrid pus from the intratracheal tube, the patient ceased breathing and his heart

stopped. He could not be revived. The now collapsed lower lobe was incised and a great pus-filled smooth-walled cavity entered. At autopsy this was revealed to be a large cyst occupying the entire lower lobe on the left.

Of the other 13 patients, 12 were well at the time of writing and had returned to a normal routine of living. The other patient, 1 of the 2 not operated on, was lost to our observation.

SUMMARY AND CONCLUSION

A group of 15 patients with pulmonary cystic disease observed in the past five years is presented. All patients in this group came to our attention because of problems referable specifically to their cystic disease. An analysis of the case histories of these patients has been made and the salient data have been analyzed.

Attention is again directed to the frequency with which cystic disease of the lung ocurs and to the fact that infected cystic disease of the lung can be and frequently is mistaken for other intrathoracic suppurative lesions, notably empyema and abscess of the lung.

Certain criteria, clinical and roentgenologic, are suggested as helpful in the recognition of cystic disease of the lung, but, in the last analysis, it is only when the possibility of cystic disease is kept in mind that this lesion will be recognized promptly and treated definitively by surgical excision.

DISCUSSION

DR. LEON J. LEAHY, Buffalo: I think that it is becoming increasingly obvious that cystic disease of the lung is a fairly common disease and to recognize it one must be alert to the appearance on roentgenograms. Unless one bears this in mind while diagnosing and treating empyema or recurrent pulmonary infection, many will be overlooked, with subsequent improper treatment that results from a mistaken diagnosis. Many large infected solitary cysts are confused with empyema. This possibility was well brought out by Maier and Haight in 1939. My colleagues and I have followed the practice for several years of obtaining a biopsy specimen of the empyemic wall in all cases. In addition to observing the occasional unrecognized cyst, tuberculous empyema is also sometimes diagnosed in this way. There are several characteristics which make one suspicious of a large cyst with empyema in the roentgenograms. These have been described repeatedly. When an infected solitary cyst exists, it has been our practice to drain these externally, as a preliminary procedure, following which a pulmonary resection or complete excision of the cyst wall is accomplished, after the infection has been controlled by this procedure. Another type of cystic disease that has attracted our attention is the multiple type that causes overdistended lungs with mediastinal herniae in very young children. These constitute more or less of an emergency in some instances in infants. Gross has reported a pneumonectomy in a 23 day old infant and Burnett a lobectomy for such a condition in a 15 day old infant. In each of these instances, the child was kept in an oxygen tent most or all of the time. We have had 3 such patients at the Children's Hospital in Buffalo, 1 of which required lobectomy at the age of 1 month and another pneumonectomy at 2 months.

The third was a child who was seen when very young, for pulmonary infection. The condition was recognized, but we decided to operate on the child at a later date, when the infection had subsided. After repeated admissions to the hospital for pulmonary infections, a pneumonectomy was done two years later. The immediate change in his appearance and activities was gratifying, and I could not help thinking that if the child had been operated on earlier his development would not have been retarded and the inconvenience and danger of repeated infections would have been avoided. I mention these because they are often confused with such conditions as spontaneous pneumothorax, diaphragmatic hernia and bronchiectasis, whereas if the underlying condition is identified and the proper treatment instituted the end result is extremely satisfactory.

Dr. Anthony R. Curreri, Madison, Wis.: Diagnostically I have been impressed by (1) the frequency of a diagnosis of empyema and the failure of the cyst to heal by drainage and (2) the failure to map out the entire lung in every case of cystic disease of the lung. Drainage of a cyst is ineffectual as long as the cyst wall is present. Therefore pulmonary resection is necessary. The failure to map out the entire lung will often result in embarrassment, because after a lobectomy other cysts will be found in either the remaining lobe or the opposite lung.

From the point of view of treatment, I have been impressed by the fact that physicians as a whole have procrastinated from radical surgical treatment in these cases because of the lack of symptoms. Early, prior to infection, a pulmonary resection would be simple, for cleavage planes would be readily available in the mediastinum. When infection supervenes, the observations in the mediastinum are altogether different. Acute inflammation is present; lymph glands are enlarged and adherent, and, as a result, individual dissection of the mediastinal structures is rather difficult. In addition, the problem of spilling purulent secretions from the involved side over to the normal lung is ever present. The mortality rate, therefore, with secondarily infected bronchogenic cysts is much higher than in cases without infection.

BLOOD DETERMINATION AND ESTIMATION OF BLOOD LOSS DURING SURGICAL OPERATIONS

NORRIS E. LENAHAN, M.D.
THEODORE A. SPITZ, M.D.
AND
DeFOREST W. METCALF, M.D.
COLUMBUS, OHIO

THE CONDITION of the surgical patient postoperatively depends on several factors, among which are surgical trauma, length of operation, type of anesthesia and loss of blood. The more closely each of these factors can be maintained to normal, the more rapid will be the patient's recovery. With improved methods of surgery and anesthesia, the causes producing shock have been reduced to a minimum, with hemorrhage or blood loss as the chief remaining cause.

Work was done to show that hemorrhage, too, could be controlled and measured and the lost blood replaced by adequate amounts to compensate for the original loss. This permits patients to be returned to the ward postoperatively in much better condition than those in whom no accurate replacement of blood has been made.

Gatch and Little [1] in 1924 observed that blood losses up to 700 cc. did not appreciably disturb the patient's postoperative course. Robust and healthy persons can lose 700 to 900 cc. of blood without showing signs of shock. However, Coller and his associates [2] expressed the opinion that in the aged, undernourished, seriously ill or bed-fast patients this does not hold true and that an equal volume of blood should be replaced.

It is agreed by all that shock occurring during or following operation is much easier to prevent than to treat. In our work we have occasion to see a high proportion of poor risk patients whose condition predispose to shock. Patients suffering from malnutrition, anemia, dehydration and chronic illnesses do not tolerate even small losses of blood without showing signs of shock.

Read at the Fifth Annual Meeting of the Central Surgical Association, Chicago, Feb. 20. 1948.

From the Departments of Anesthesia, St. Anthony Hospital, Columbus, Ohio, and Veterans Hospital, Dayton, Ohio.

1. Gatch, W. D., and Little, W. D.: Amount of Blood Lost During Some of the More Common Operations, J. A. M. A. **83**:1075 (Oct. 4) 1924.

2. Coller, F. A.; Crook, C. E., and Iob, V.: Blood Loss in Surgical Operations, J. A. M. A. **126**:1 (Sept. 2) 1944.

Blain [3] in 1929, Coller and Maddock [4] in 1932 and Pilcher and Sheard [5] in 1937 made extensive measurements on blood loss and concluded that the volume lost was always greater than the surgeons estimated and that circulatory volume may be decreased considerably before clinical signs of shock are noted. Leriche and Vasilaros [6] in 1939 concluded that a loss of even 500 cc. was not a matter of indifference to a body that is called on to effect the repair of trauma and disease.

There are two methods of measuring blood loss in surgical operations, namely, colorimetric and gravimetric. We were primarily interested in a method which would indicate the actual blood loss at any given

TABLE 1.—*Data on Blood Loss in Two Hundred and Seventy Operations*

Operations	Number of Cases	Blood Loss, Cc.		
		Minimum	Maximum	Average
Hernia	20	25	75	40
Appendectomy	20	25	50	35
Hemorrhoidectomy	20	25	150	55
Salpingectomy	25	80	225	150
Hysterectomy	25	155	375	300
Thyroidectomy	10	75	200	125
Biliary	10	75	525	300

TABLE 2.—*Data on Blood Loss in Seventy-Seven Cases*

Operations	Number of Cases	Blood Loss, Cc.		
		Minimum	Maximum	Average
Gastric resections	12	320	780	503
Intestinal resections	10	510	1,425	769
Abdominal perineal resections	10	415	2,420	1,080
Vagotomy	10	165	690	423
Suprapubic prostatectomy	10	265	1,235	551
Transurethral resections	15	172	855	563
Nephrectomy	10	285	845	478

stage in the surgical procedure, and the gravimetric method is the technic which would enable us to do this. Wangensteen [7] in 1942

3. Blain, A.: Impressions Resulting from Three Thousand Transfusions of Unmodified Blood, Ann. Surg. **89**:189, 1929.

4. Coller, F. A., and Maddock, W. G.: Dehydration Attendant on Surgical Operations, J. A. M. A. **99**:875 (Sept. 10) 1932.

5. Pilcher, F., and Sheard, C.: Measurements on the Loss of Blood During Transurethral Resection and Other Surgical Procedures, Determined by Spectrophotometric and Photelometric Methods, Proc. Staff Meet., Mayo Clin. **12**:213, 1937.

6. Leriche, R., and Vasilaros, E.: De la perte de sang occasionée par les diverses opérations: Contribution à l'étude de la maladie postopératoire, Mém. Acad. de chir. **65**:1242, 1939.

7. Wangensteen, O. H.: Controlled Administration of Fluid to the Surgical Patient, Minnesota Med. **25**:783, 1942.

made the first gravimetric studies and showed that this was a rapid and accurate method for determining blood loss as it occurred, so that replacement could be effected immediately. The method consisted of weighing the dry sponges as they were given to the scrub nurse. The surgeons were fully cooperative in using wet sponges only when absolutely necessary. In most instances the wet sponges were disregarded in the total estimates. As the blood-stained sponges were removed from the operative field they were again weighed, and the difference in weight was recorded on a blood loss chart. The blood in the suction bottles was also measured. A curve was plotted indicating the amount of blood lost by operation and gained by trans-

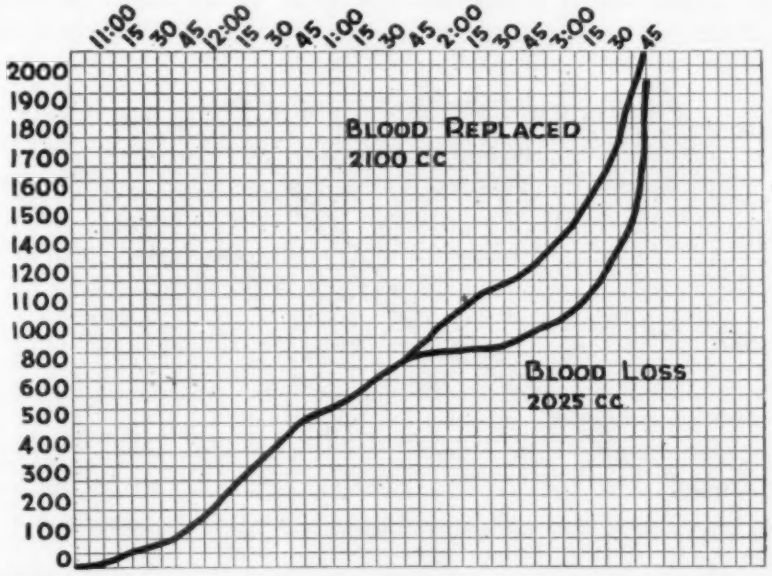


Fig. 1.—Graph of blood loss and replacement in a case of gastric resection.

fusion during the entire course of the operation. The amount of blood lost on the drapes and surgeon's gowns and gloves was not measured during the course of the operation, but transfusion was maintained at approximately 100 to 200 cc. above the calculated loss to provide for this as well as for the removal of organs containing blood.

The accompanying graphs show how the number of cubic centimeters of blood lost can be determined at any moment during an operation.

We measured the blood loss during two hundred and seventy major operations. Clinically the results in most short procedures were not striking.

Herniorrhaphies and appendectomies were significant in that the blood loss was rather small. Patients with hemorrhoidectomies, sal-

pingectomies and thyroidectomies averaged about 125 cc. blood loss. The average blood loss for ten biliary operations was 300 cc.

Gastric and intestinal resections showed a surprisingly low figure. The average loss for twelve gastric resections was 503 cc. Prior to this study we had been giving patients undergoing gastric resection 1,500 to 2,000 cc. during the course of operation which averaged four hours. The administration of fluids in excess of tissue requirements can be of serious consequence especially in the aged persons, in patients suffering from cardiac disease, with or without decompensation, and in chronic pulmonary and renal disease. The major blood loss in abdominoperineal resection is during the perineal procedure. In ten operations, the average blood loss for the abdominal procedure was 281 cc. ; for the perineal resection it was 654 cc. It is generally

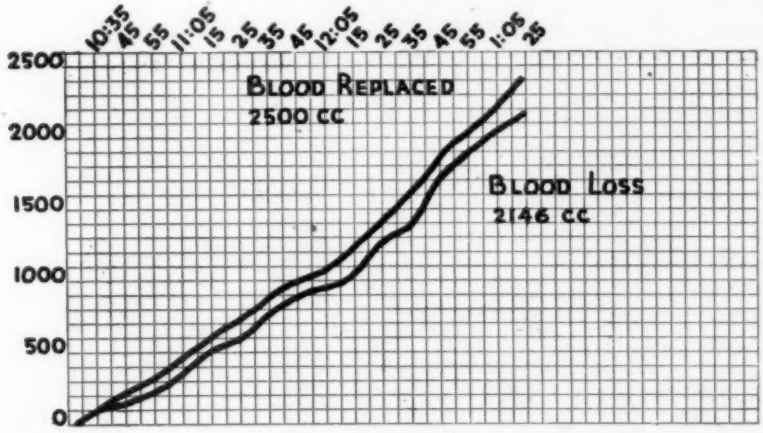


Fig. 2.—Graph of blood loss and replacement in a case of pneumonectomy.

agreed that the change in position of the patient for the perineal procedure is a major shock-producing factor, and this combined with unreplaced blood loss may prove to be of serious consequence and produce a dramatic drop in blood pressure.

In vagotomy there was an average blood loss of 423 cc. In our series of ten nephrectomies blood loss averaged 478 cc. In suprapubic prostatectomy in a series of 10 cases there was a rather pronounced loss at the time of operation, averaging 551 cc. It has been estimated by Pilcher and Sheard [5] that the patient will lose as much in the twenty-four hours postoperatively as he did at the time of the operation. Blood loss in our series of transurethral resections averaged 563 cc. This loss when added to the loss of blood during the next twenty-four hours results in a considerable amount of blood lost, especially for the age group in which these operations are usually

performed. The surgeon and the anesthesiologist should take this into consideration when computing blood loss.

The estimation of blood loss in transurethral resections was made by the colorimetric or photelometric method. A Leitz photelometer was used. It is used clinically for the determination of the grams of hemoglobin per hundred cubic centimeters of blood by placing a measured amount of blood (0.1 cc.) in 20 cc. (a dilution of 1 to 200) of a 1 per cent aqueous solution of sodium carbonate.[8] The solution is placed in a spectroscopic absorption cell of 1 cm. internal thickness and inserted in the photelometer. By the use of proper spectral filter and determination of the amount of light transmitted by the solution of blood, it is possible to convert the readings of the microammeter into equivalent grams of hemoglobin. In turn, if the photelometric reading for any diluted sample of blood is made and the equivalent

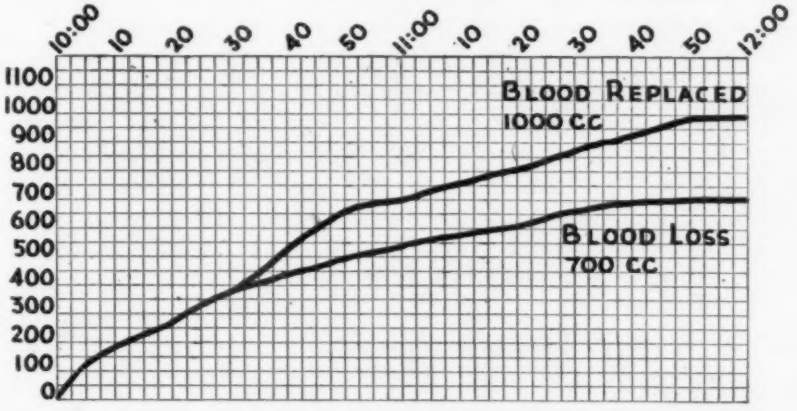


Fig. 3.—Graph of blood loss and replacement in a case of excision of the thymus.

degree of dilution in terms of the standard (1 to 200) and the hemoglobin value (grams per hundred cubic centimeters) of the subject are known, it is obvious that the amount of blood recovered during operations can be determined by the expression:

$$\frac{\dfrac{\text{Volume (cc.) irrigating water}}{200} \times \text{photelometric reading of irrigating water}}{\text{Value of patient's hemoglobin (grams per 100 cc.)}} = \text{cubic centimeters of blood lost}$$

During transurethral resections[9] all the irrigating water is collected in large bottles or buckets, thoroughly mixed and measured as to the amount. A sample was then placed in photelometer and the number of cubic centimeters of blood lost was estimated.

8. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: The Photelometer and Its Use in the Clinical Laboratory, Am. J. Clin. Path. **3**:405, 1933.

9. Nesbitt, R. M., and Longer, K. K.; Studies of Blood Loss During Transurethral Resections, J. Urol. **46**:713, 1941.

TABLE 3.—*Data on Blood Loss in Thoracic, Orthopedic and Neurologic Operations*

Operations	Blood Loss, Cc.	Number of Cases	Blood Loss, Cc.		
			Minimum	Maximum	Average
Thoracic		23	450	3,050	2,073
Intrathoracic (11)	1,425				
Esophagogastrostomy					
Resection tumor of esophagus; esophagogastrostomy; splenectomy	2,375				
Lobectomy (7)					
Left lower (5)	1,995				
	2,100				
	1,900				
	3,050				
	2,280				
Right lower (2)	2,375				
	2,565				
Pneumonectomy, I (2)	1,710				
	2,090				
Thoracic wall (12)					
Rib resection, exploration of sinus	450				
Thoracic					
Thoracic wall					
Thoracoplasty (11)	715				
	1,235				
	1,045				
	2,565				
	1,425				
	860				
	1,125				
	955				
	875				
	1,245				
	960				
Orthopedic		25	310	2,540	812
Amputation, midthigh (4)					
Tourniquet (1)	190				
No tourniquet (3)	480				
	455				
	315				
Bankart (2)	1,045				
	950				
Dorsal spine fusion (3)	1,235				
	855				
	715				
Revision spinal fusion	310				
Hip, S-P pin (5)	2,790				
	1,135				
	775				
Femur (6)					
Bone graft (2)	2,540				
	1,600				
Open reduction (2)	405				
	855				
Saucerization (2)	715				
	1,900				
Tibia (2) Bone graft (2)	475				
	665				
Neurologic		12	125	1,520	541
Cerebellar craniotomy (1)	1,520				
Cervical laminectomy (1)	1,045				
Dorsolumbar sympathectomy (1)	950				
Lumbar sympathectomy (4)	125				
	180				
	225				
	330				
Lumbar hemilaminectomy (5)	315				
	255				
	450				
	420				
	675				

Neurosurgical, intrathoracic and orthopedic procedures were particularly impressive, in that blood loss was known to be great but could rarely be estimated correctly within 500 cc. Before our study we occasionally saw early signs of shock during these operations, indicating that we were behind in our replacement therapy. This was most frequently observed during orthopedic operations where the use of a tourniquet was not possible or permissible.

It is interesting to note that the blood loss in midthigh amputations done with a tourniquet was less than half than those in which no tourniquet was used. Since these estimations have been carried out and adequate replacement instituted we rarely see signs of shock due to blood loss in orthopedic cases. Blood loss in laminectomies was found to average 1,082 cc.

We do not undertake intrathoracic operation without having 5 units of whole blood available for the patient.[10] The average blood loss for lobectomy, pneumonectomy and esophageal operation in our series of 25 cases was 2,073 cc. The duration of these operations varied in length from four to eight hours. Most of these patients are not good risks and tolerate comparatively small losses of blood poorly. In patients undergoing thoracoplasty the blood loss will vary with the stage of the procedure, being higher for the first stage and considerably lower for the third. The over-all average for eleven operations was 1,182 cc. This does not include the 1 death due to massive rapid hemorrhage of over 4,500 cc.

The blood loss in neurosurgical treatment is highest for intracranial procedures.[11] During operations on the spinal column or spinal cord 500 cc. of whole blood should be administered. Unfortunately, at St. Anthony and the Veterans Hospitals there are few neurosurgical operations performed, and consequently our series of cases is rather small. However, we believe that there are enough cases so that one can form an opinion of the blood loss in this type of operation. More work will be done in order to build a larger series, which may reflect more accurately the blood loss in neurosurgical treatment.

CONCLUSIONS

1. Major operations result in considerable blood loss. The amount of blood loss depends on the type of operation, attention to hemostasis and duration of the operation. The time required to perform an operation is exceedingly important.

10. White, M. L., and Buxton, R. W.: Blood Loss in Thoracic Operations, J. Thoracic Surg. **12**:198, 1942.

11. White, J. C.; Whitlaw, G. P.; Sweet, W. H., and Hurwill, E. S.: Blood Loss During Neurosurgical Operations, Ann. Surg. **107**:287, 1938.

2. The effect of blood loss depends on the relationship of the amount lost to the total blood volume, the rapidity of loss and the preoperative status of the patient.

3. The only accurate estimation of blood loss is by direct measurement.

4. The gravimetric method of calculation of blood loss enables one to follow and replace the loss as it occurs.

5. Knowledge of blood loss obviates the possibility of insufficient or excessive replacement therapy.

Margaret Lacy, Alice Ollic and Sister Adelpha and her group assisted in the preparation of laboratory data at St. Anthony Hospital.